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PUBL. JUNE 1952

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ITS CLINICAL INTERPRETATION

BY

Joseph M. Barker, M.D., F.A.C.P.

Cardiologist, Yater Clinic; Associate Professor of Clinical Medicine, Georgetown University School of Medicine; Director of the Heart Station and Visiting Physician, Georgetown University Hospital; Chief of Cardiology, Gallinger Municipal Hospital; Consulting Cardiologist, Arlington Hospital, Arlington, Virginia.

Assisted By

Joseph J. Wallace, M.D., F.A.C.P.

Advised By

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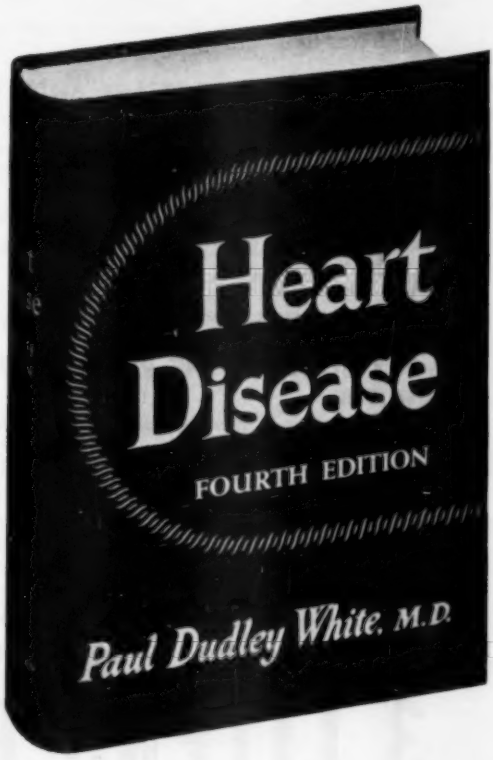

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2. Pelner, L., and Waldman, S.: Am. Pract. *3*:293 (Apr.) 1952.

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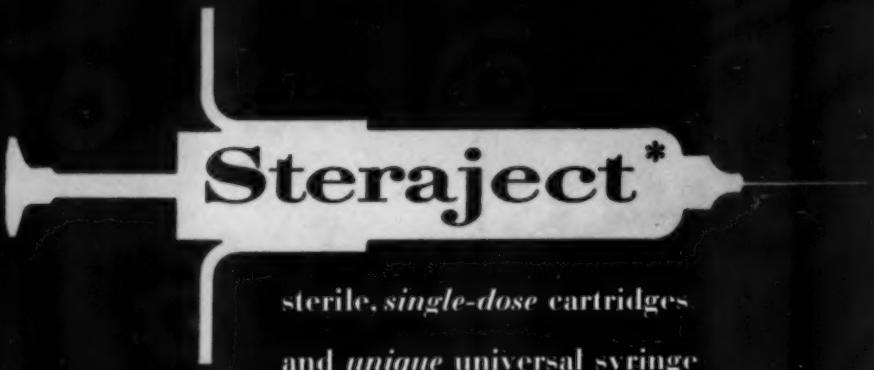

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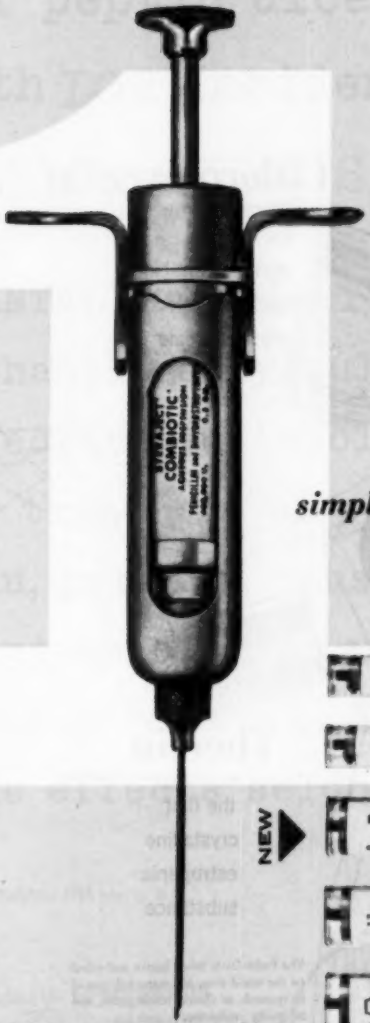

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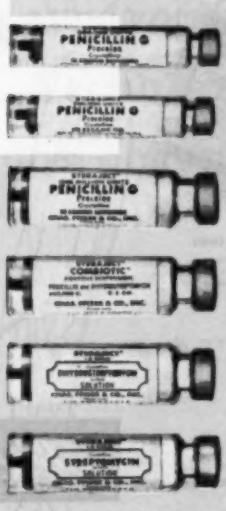

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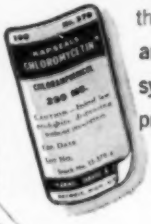

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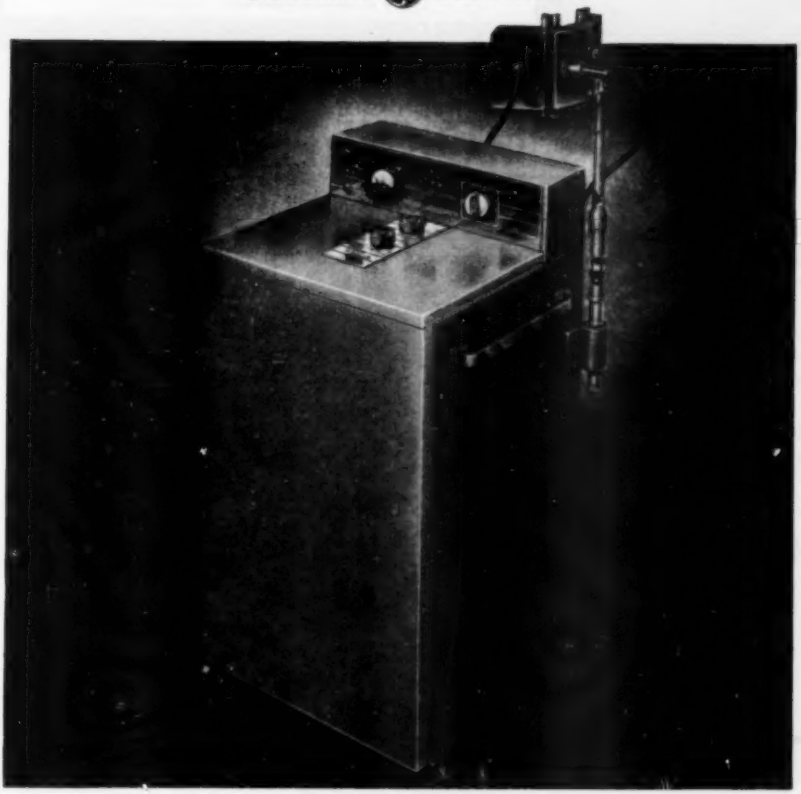

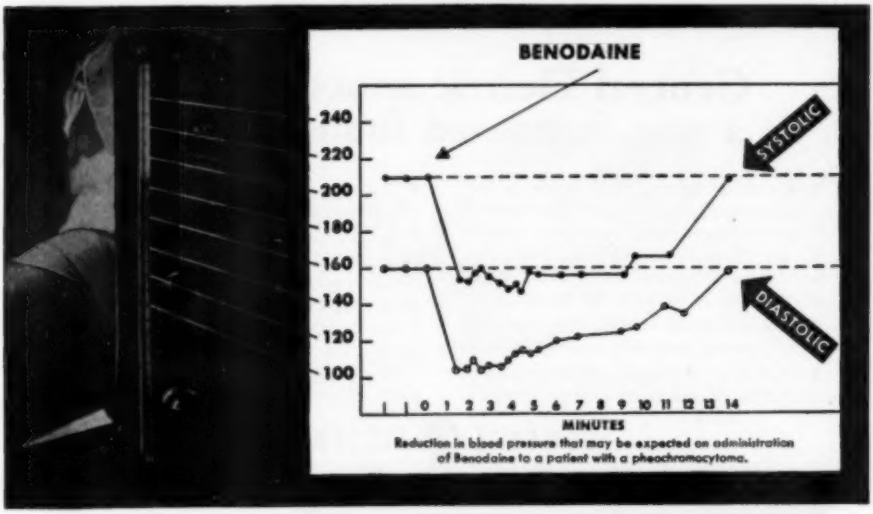

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1. Becker, M.C., Bass, R.D., and Robbins, C.M., *Postgraduate Medicine* 6:408–412, November 1949.
2. Goldenberg, M., and Aranow, H. Jr., *J.A.M.A.* 143:1139, July 29, 1950.
3. Calkins, E., Dana, C.W., and Howard, J.E., *J.A.M.A.* 145: 880, March 24, 1951.

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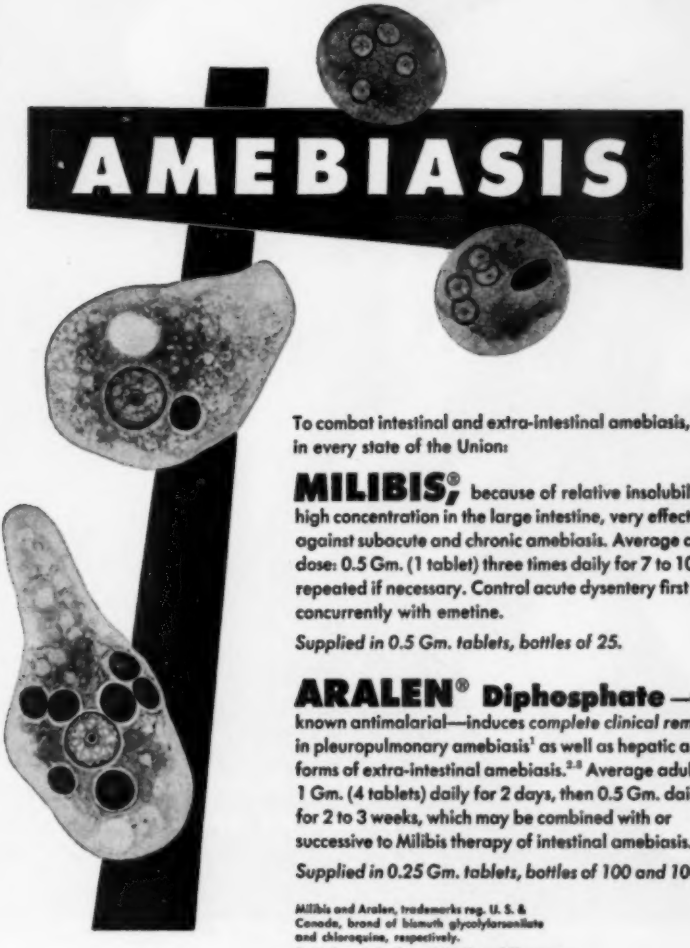

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1. Lindsay, A. E., Gossard, W. H., and Chapman, J. S.: *Dis. Chest*, 20:533, Nov., 1951.
2. Conan, N. J., Jr.: *Am. Jour. Med.*, 6:309, Mar., 1949.
3. Emmett, J.: *J.A.M.A.*, 141:22, Sept. 3, 1949.

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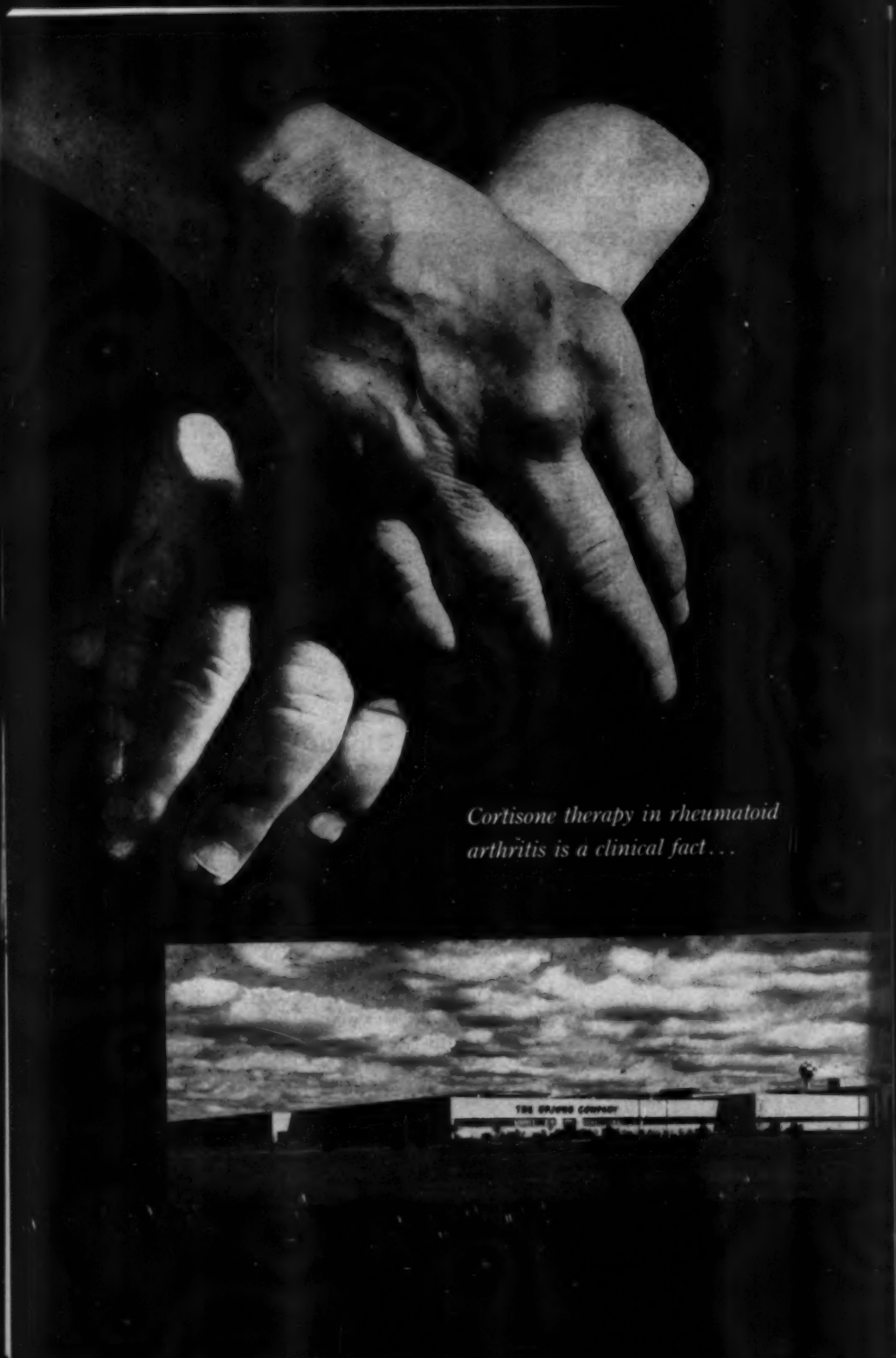
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INDICATIONS

The drug is of value in essential hypertension with fixed levels and early malignant hypertension, its effectiveness often being more marked in severe (although not terminal) phases of these disorders. It is most effective in hypertension persisting or recurring after sympathectomy.

Preliminary studies indicate worthwhile results in toxemias of pregnancy and in acute glomerulonephritis. When renal damage is advanced, as in chronic renal hypertension and chronic glomerulonephritis, the value of the drug is considerably less and it may be hazardous if not used with extreme caution.

MANNER OF USE

It is essential that the physician undertaking the prescribing or administering of Apresoline realize that the dosage requires individualization. In general, the response of each patient should be a guide to appropriate adjustment and spacing of doses.

The Ambulatory Patient

Therapy should be initiated with the *oral* form. Careful and detailed instructions should be given so that the patient will know what subjective response to expect. Within 12 to 24 hours after the first dose, headache and palpitation may occur. Often, these symptoms will disappear spontaneously with no change in dosage within 7 to 10 days, or can be ameliorated with adjunctive therapy.

Patients should be observed at frequent intervals by the physician, not only to check on the status of the blood pressure and other physiologic responses, but also to determine whether dosage change is warranted.

The initial dose of Apresoline for the average ambulatory patient with a moderate to severe degree of hypertension should be not more than 25 mg. This should be given after the morning meal and repeated after lunch, after dinner, and at bedtime. The *total* daily dose (100 mg.) is continued for one week unless side effects justify discontinuing medication. During the second week, the dose may be increased to 50 mg. four times daily (after each meal and at bedtime). This new total daily dose (200 mg.) may be continued throughout the second week.

Provided side effects are absent or minimal and the patient's blood pressure should be further reduced to a more desirable level, the single dose of Apresoline may be raised to 75 mg. four times daily for the third week, and 100 mg. four times daily for the fourth week.

Many patients obtain maximal benefit from 100 mg. of Apresoline four times daily. Some individuals are best stabilized with as little as 100 mg. daily in divided doses, while others require as much as 600 mg. daily in four equal doses.

The Hospitalized Patient

With the more severe types of hypertensive disease, 25 mg. of Apresoline may be administered *orally* every 6 hours for the first 24 hours. Thereafter, the individual doses, still at 4-6 hour intervals, are increased by 25 mg. daily until the desired effect is obtained. The average *daily* dose is 400 mg. with a range from 100 mg. to approximately 600 mg.

It has been recommended that the blood pressure be taken just prior to and one hour after each dose to determine optimal hypotensive responses and thereby, the optimal daily dose.

The *parenteral* form of Apresoline is to be used only for coma or other conditions in which the preparation cannot be taken orally. The usual dose is 20 to 40 mg. given intravenously or intramuscularly, but (especially in patients having marked renal damage) a smaller initial dosage may be indicated. Dosage increment for parenteral administration must be adjusted with even greater care than that for oral administration. The patient's blood pressure should be checked frequently after such injections, for in some cases there may be a rather precipitous drop. The pressure may begin to decline within 2 or 3 minutes after injection, the average maximal fall occurs at 25 minutes (range 10-80 minutes). If there is increased intracranial pressure, lowering the blood pressure further may result in marked cerebral ischemia. Because of this possibility, withdrawal of a suitable amount of spinal fluid may be considered. In most instances it will be possible to shift to oral therapy with Apresoline within 24 to 48 hours.

In cases of *preeclampsia or eclampsia* the blood pressure may fall dramatically to normal within 5 to 10 minutes after the intravenous injection of 20 to 40 mg. of Apresoline. The pressure has remained within normal limits for periods of 6 to 25 hours in some cases. If pressure rises again, additional parenteral doses of Apresoline may be administered.

SIDE EFFECTS

Considerable difficulty can be obviated and treatment facilitated by judiciously forewarning the patient of possible, usually transitory, side effects. This is particularly true in the case of postural hypotension and its associated effects of palpitation, headache, and nausea. In addition, certain side effects are necessarily associated with reduction of the blood pressure to more normal levels—the very purpose for giving Apresoline. In the case of postural hypotension, the patient should be told to rise slowly from a recumbent position, etc.

The cooperation of the patient will be optimal when he is taken into the physician's confidence and understands that any unpleasant effects will probably be only temporary and, if possible, should be endured to obtain the desired beneficial results. Judicious forewarning need not excite apprehension and may actually be a factor in obtaining a satisfactory effect.

The most frequent side effects include mild to severe headache, postural hypotension, tachycardia, palpitation, dizziness, weakness, nausea and vomiting. Somewhat less common are: numbness and tingling of the extremities, flushing, varying degrees of nasal congestion, lacrimation and conjunctival inflammation. A few cases of skin rash have been reported, indicating an individual sensitivity.

As Apresoline is continued, these untoward effects generally subside. If nausea or vomiting become troublesome, antacids may provide considerable relief.

Less Frequent Side Effects

Dyspnea and anginal symptoms have occasionally been reported in patients with coronary disease. The drug should be used with caution in the presence of coronary disease. Notably, however, in *some* patients having coronary disease, Apresoline has relieved anginal symptoms.

When Apresoline is given to some sympathectomized patients, they may complain of an excessively frequent urge to defecate.

If the dosage of Apresoline is increased too rapidly, especially in patients with more severe forms of hypertension and uremia, certain cerebral symptoms may accompany the fall in blood pressure. Such symptoms have been reported to range from mild anxiety or depression to acute anxiety states or severe depression and coma.

Headache

Approximately 40 per cent of patients receiving Apresoline experience mild to severe headache during the first days of treatment. Generally, it seems to be centered in the occipital region, and has been described as "pounding and grinding." The headache may not be due to any direct action of the drug, but rather to an indirect result of the lowered blood pressure or even an antihistaminase action, preventing the normal destruction of histamine. Actually, the symptoms of the same type of headache can be induced by histamine. Symptoms can frequently be relieved by the use of antihistamine drugs.

It has also been suggested that some of the headache may be due to a general vasodilatation of certain cerebral or centrally located vessels, as in congestive migraine. Therefore, a number of clinicians have found that ergotamine tartrate, "in extremely small amounts," provides satisfactory control.

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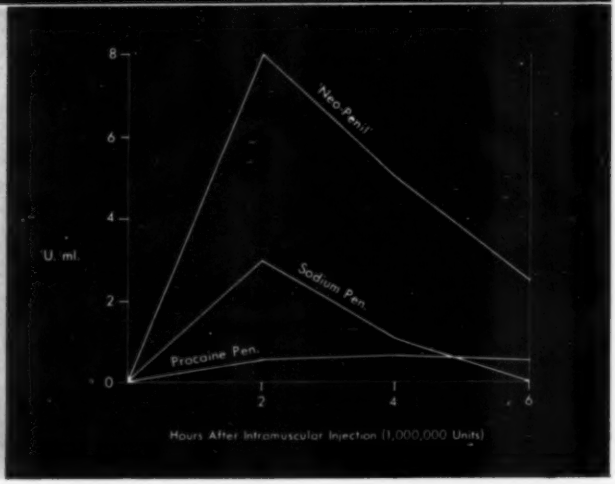

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1. Lancet *1*:1255 (June 9) 1951.

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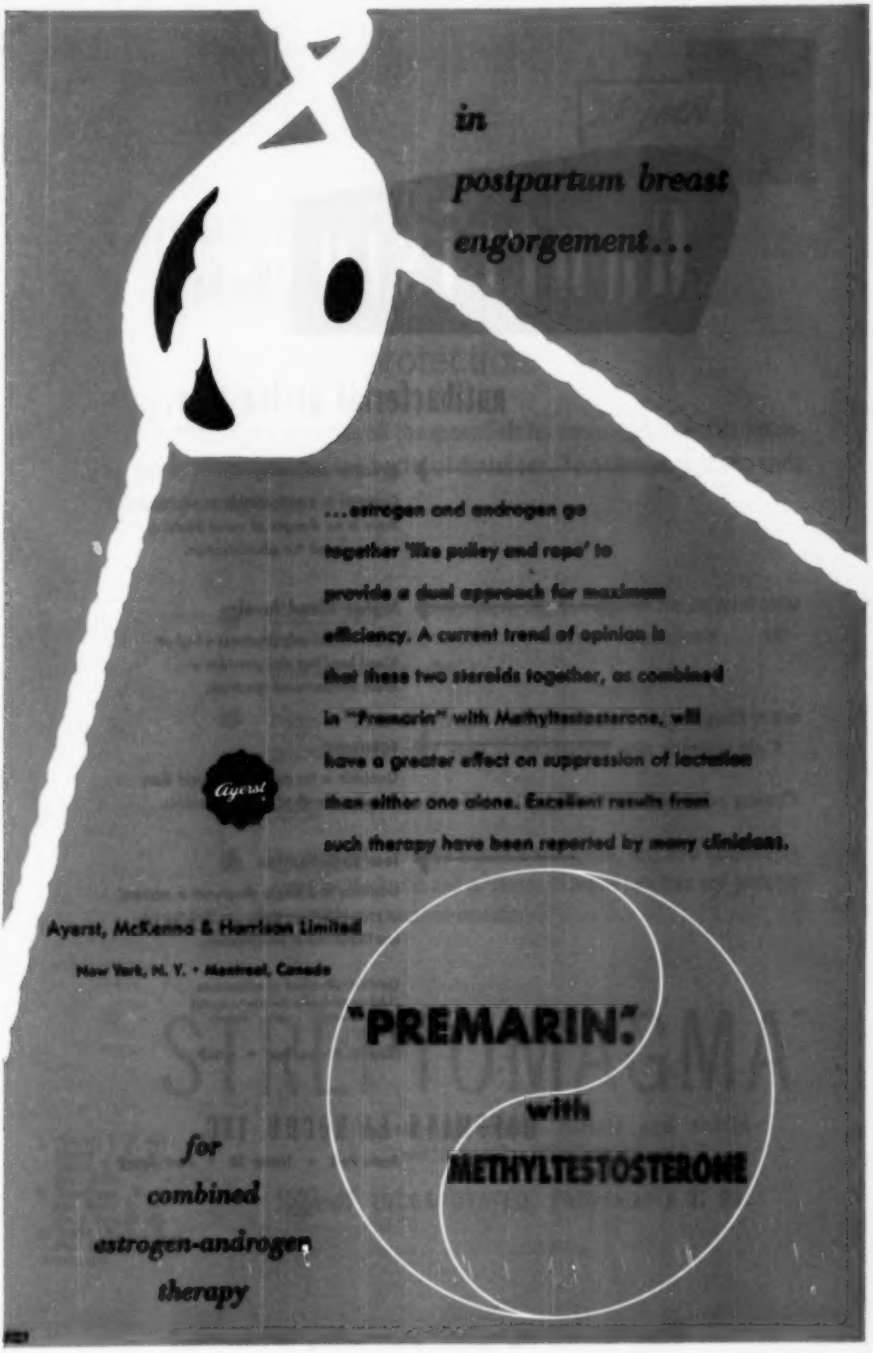
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1. Pulaski, E. J. and Connell, J. F., Jr.: Bull. U. S. Army M. Dept. 9:265.
2. Wooldridge, W. E. and Mast, G. W.: Am. J. Surg. 78:881.
3. Swalm, W. A.: M. Rec. 140:26.

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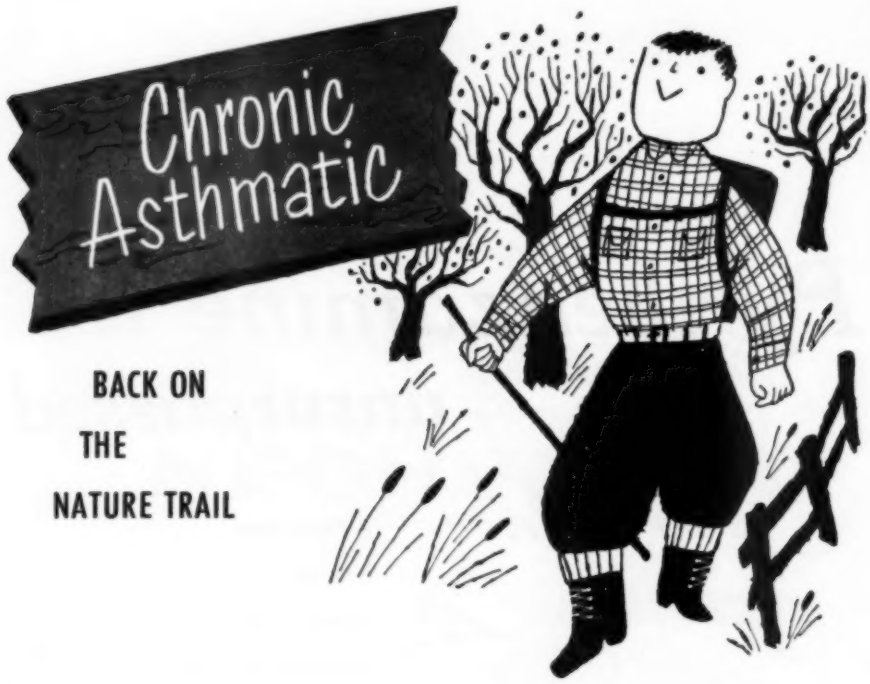

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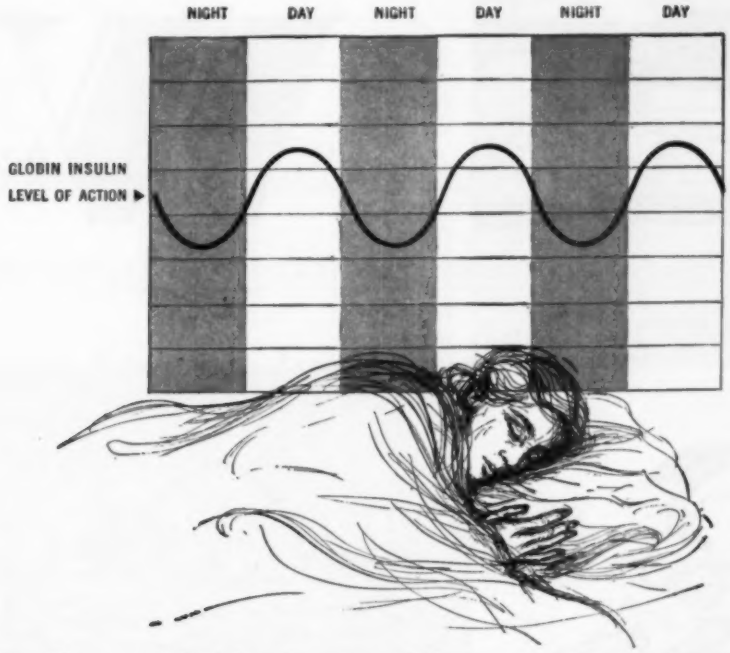

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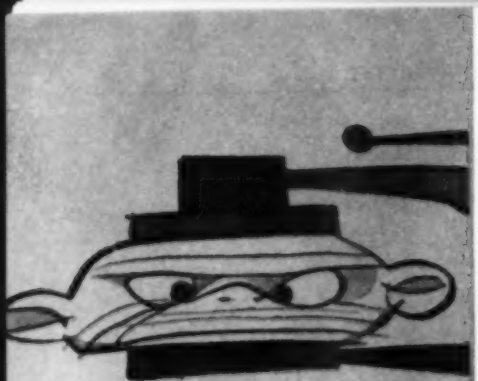
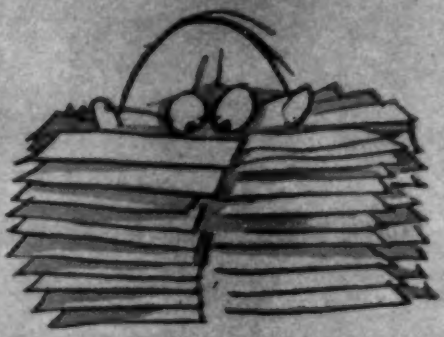


pressure

When

diet



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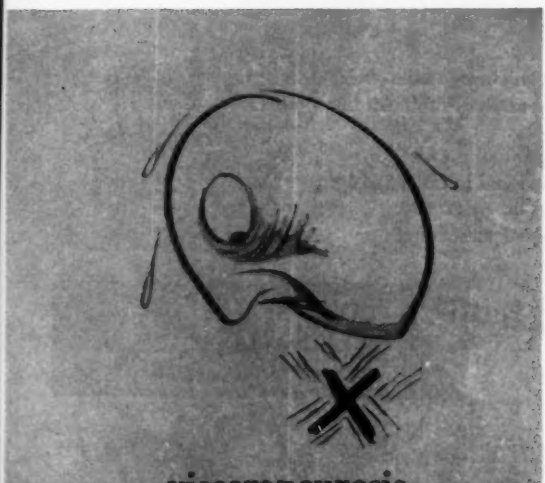

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1. Hock, C. W.: J. Med. Assn. Ga. 40:22, 1951 • 2. Hufford, A. R.: J. Mich. St. Med. Soc. 49:1308, 1950 • 3. Chamberlin, D. T.: Gastro-

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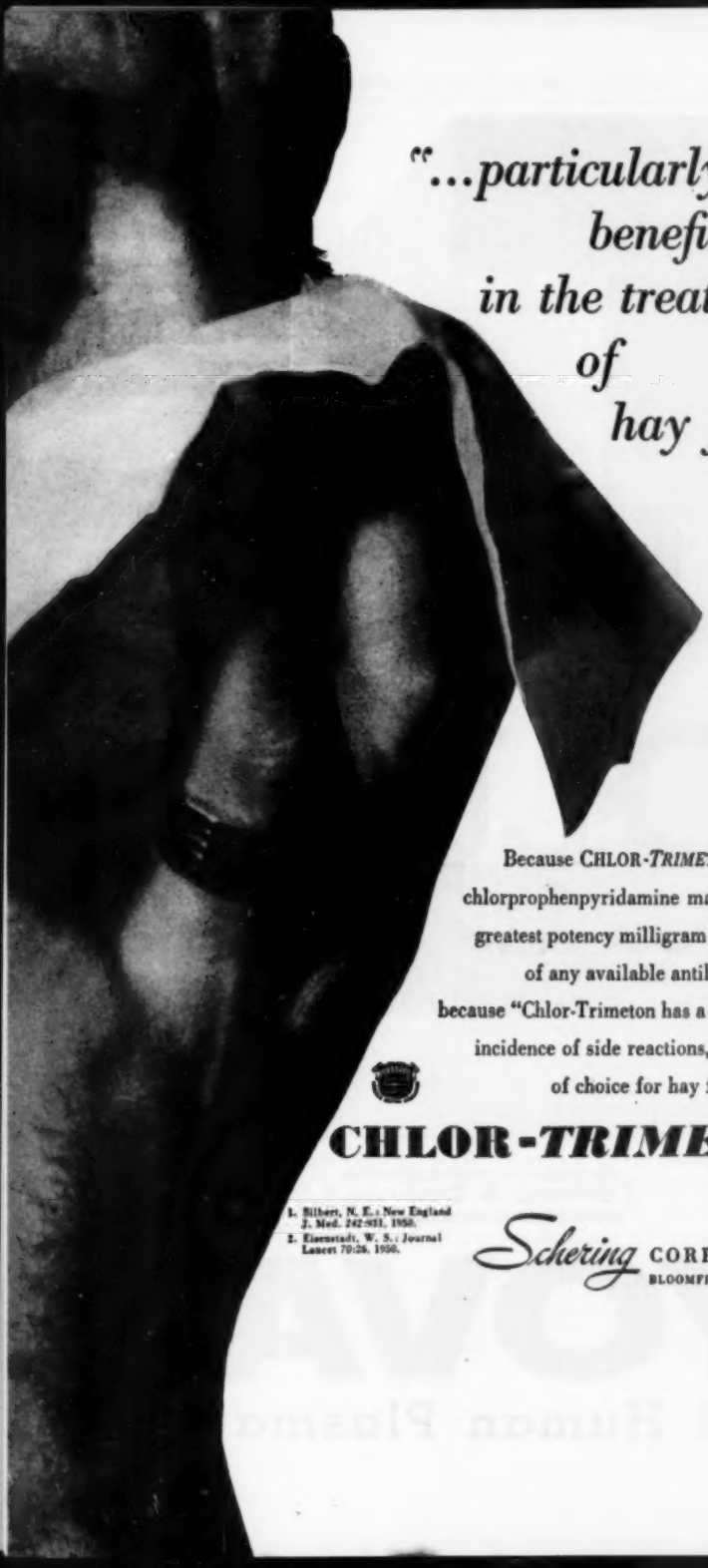

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1. Silbert, N. E.: New England J. Med. 242:931. 1950.
2. Eisenstadt, W. S.: Journal Lancet 70:28. 1950.

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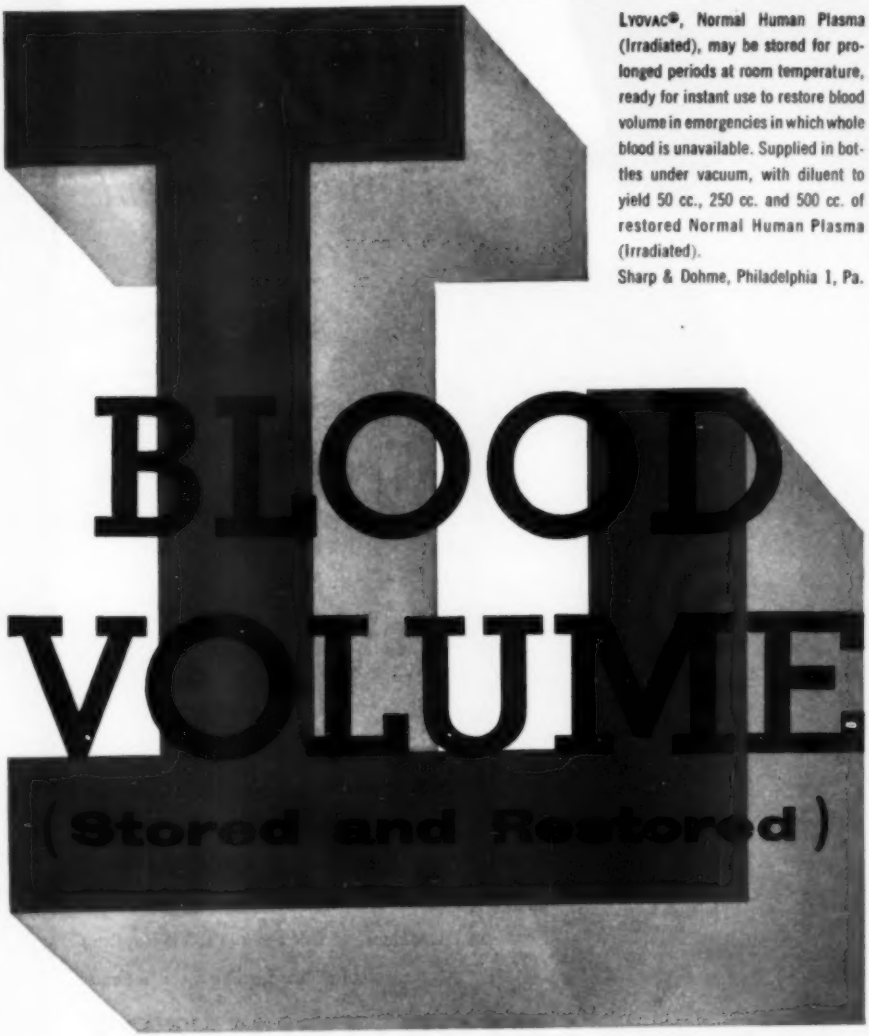

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ANNALS OF
INTERNAL MEDICINE

VOLUME 37 JULY, 1952 NUMBER 1

IMMUNITY TO POLIOMYELITIS*

By JAMES GEAR, *Johannesburg, South Africa*

THE Board of Regents of the American College of Physicians has conferred a great honor on me and on the University and the Institute, which I represent, and on the country from which I come, in selecting me to give the James D. Bruce Memorial Lecture in Preventive Medicine. I am very proud indeed to receive this high award from the distinguished President of your famous College, yet I feel very humble as I stand before you thinking of those eminent men who have preceded me in this office. Dr. James S. Simmons, Dr. Stanhope Bayne-Jones, Dr. Karl F. Meyer and Dr. Rolla E. Dyer, each brought the luster of a famous name and the experience of a long and brilliant life devoted to the service of Preventive Medicine to this commemoration. I have no such claim on your attention, yet because he was a man of exceptionally wide sympathies I like to think that Dr. James Bruce would have welcomed me here. His interests ranged far beyond the national boundaries of the United States of America, and I am sure he would have been particularly interested in immunity to poliomyelitis, one of the outstanding problems in Preventive Medicine. Then, too, like him I come from one of the Nations of the British Commonwealth. He came from Canada. I come from South Africa, until recently a little known, far-off land. Because it is relevant to my theme, I will describe briefly the history and the present situation in that country.

This month the people of South Africa celebrated the tercentenary of the land of Jan van Riebeek to establish the first European settlement at the Cape of Good Hope, of which Sir Francis Drake wrote, as he sailed round the world many years before, "This Cape is a most stately thing and the fairest Cape we saw in the whole circumference of the earth." It was then called the Cape of Storms. The Cape of Storms, the Cape of Good Hope—two different names for the same Cape—epitomize the character of the South

*James D. Bruce Memorial Lecture, presented at the Thirty-third Annual Session of the American College of Physicians, Cleveland, Ohio, April 21, 1952.
From the South African Institute for Medical Research, Johannesburg.

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Africa that has grown in the 300 years since that first settlement. It is a land of contrasts, where Western Europe rubs shoulders with primitive Africa. It is a land of black and white.

From the settlement which Jan van Riebeek established, where Cape Town now stands, the settlers and their descendants extended the colony ever farther northward and eastward until they occupied almost all of what is now called the Cape Province. Then from the Cape Colony, as it became,

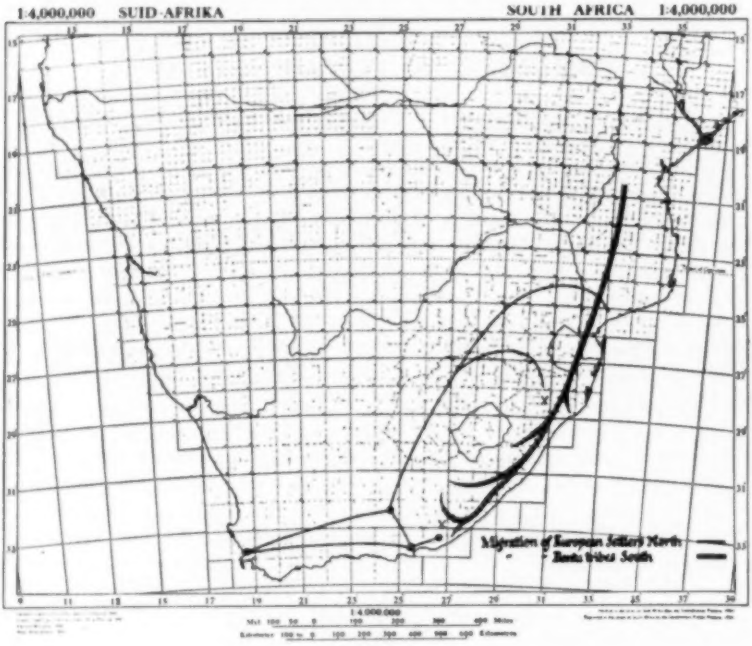


FIG. 1.

groups of the settlers trekked into the interior of the sub-continent to occupy the land which had recently been depopulated by the ravages and the fear of Chaka the great Zulu King, the "Black Napoleon of South Africa" (figure 1).

On their journeys these European pioneers or Voortrekkers came into contact with the blacks, or Bantu, who arrived in South Africa from the north as the whites arrived from over the sea in the south. Where the two waves met there was friction and there were often clashes. Then after several bloody battles they mutually agreed that the country was big enough for both and there was room for each in his own territory, and there has been peace between the whites and the blacks in South Africa for nearly three-quarters of a century.

"Distant hills are always green and the best gold lies further on" was the motto of many of those who followed in the footsteps of the Voortrekkers. Many found the fortunes they came to seek, for here were the richest diamond and goldfields in the world. They founded cities which today compare with any in the world.

Of the 2,500,000 Europeans at present in South Africa, approximately two-thirds live in these cities and towns, often in fine houses. Here they enjoy all the amenities of civilization, and, not least, they have a varied mixed diet and a purified water supply, and their dwellings are provided with water-borne sewerage. The other one-third live in the country under rural conditions. Their standard of living generally is also high.

Most of the Bantu remained in and still today occupy the land of their forefathers, where no white man may settle or own land. In these Territories they have largely retained their ancestral customs and ways of living, except that their once regular resort to tribal warfare is not encouraged. Here their primitive dwellings form an attractive feature of the landscape; the Zulus in their beehive-like grass huts; the Xosas in their mud-walled thatched huts in the Transkei; the Basutos in their stone-walled houses in Basutoland. They are clean and tidy people, but, as with most primitive people, there is no provision for the disposal of excreta. They get their drinking water from heavily polluted rivers and streams and they drink it without any purification. Their staple diet is maize meal.

But a large number of them have left the land of their forefathers to settle in the neighborhood of European towns, to help the European dig for diamonds, mine the gold, and, latterly, work the machines of the factories. Indeed, an ever increasing proportion of them, attracted by the money to be earned, the bright lights and the excitement of the city, are forsaking their lands, their villages, their tribes and the ways of their ancestors, to work in industry. For South Africa is in the throes of an industrial revolution. This is the tragedy of the Bantu people, for their townships, colloquially known as locations, have grown mushroom-like and slums have developed, and even now many of the consequences of overcrowding are upon us.

So it has come to pass that in South Africa there are two distinct sections of the population, distinct in origin, habits, customs and ways of living. But Western European and American civilization is gradually overwhelming and replacing the cultures of the native people. Primitive Africa is passing away, but even yet the opportunity remains to study the characteristics of the people under the influence of these primitive cultures, and the effects of the transition to the ways of Western Europe.

There are many virtues and advantages in the primitive life. Not least among them is a relative freedom from many of the maladies which afflict those enjoying the amenities of civilization. Because the opportunity of comparative study is passing and will never return, attention has been increasingly given by those concerned to the relative incidence and im-

portance of certain ailments in the European and African. Higginson [1] has warned against such comparisons as have been made in the past. Many of them are invalidated because of neglect to compare age group with corresponding age group. It is clear, however, that pernicious anemia, coronary thrombosis, acute appendicitis, peptic ulcer and gastric carcinoma are rare in the Bantu, but occur as frequently in the European South African as in his cousins in Europe or America. To take one example, Higginson has seen only two cases of ischemic heart disease resulting from coronary thrombosis in 300 postmortem cases of heart disease in the Bantu. Whether this is because the African has a sunny, happy-go-lucky nature, or whether it is because his staple diet lacks many of the ingredients of the richer diet of the European, or whether it is because his skin is black, is not known. It obviously is a matter deserving of further study, as is also the fact that primary carcinoma of the liver and Kaposi's sarcoma are much more frequent in the Bantu than in the European. The study of these differences may yield valuable information about the causation and hence about the prevention of these conditions (table 1).

TABLE I
Incidence of Disease

Common in Europeans Uncommon in Bantu	Uncommon in Europeans Common in Bantu
Pernicious anemia	Primary carcinoma of liver
Coronary thrombosis	Kaposi sarcoma
Acute appendicitis	Hemosiderosis
Peptic ulcer	Epidemic typhus fever
Gastric carcinoma	Tuberculosis

In the case of the infective diseases, it is understandable why tuberculosis and typhus fever are more prevalent in the Bantu. It is not so clear why, until recently, diphtheria was less prevalent, but studies by Murray [2] and Mason [3] have given us clues to the reason. They have found that, although the clinical disease is less frequently seen, infection is more widespread and so is immunity to the disease.

It was against this background that we undertook our study of poliomyelitis in South Africa. It was considered that it would be of value to study the effect of the diverse conditions of country, climate, people and their ways of living on the incidence of poliomyelitis. It was expected that significant differences would be revealed.

It is of interest to recall that the first record of a case of paralytic poliomyelitis comes from Africa—from ancient Egypt. It is on a plaque now in the collection of the Ny Carlsberg Glypotek in Copenhagen—the stele of Ruma, which dates from the Thirteenth Century before Christ and shows a man with a crutch and a withered limb (figure 2). A reproduction of this plaque formed the badge of the Second International Poliomyelitis Conference. Then, too, it is of interest to recall that the first record of an epidemic of poliomyelitis is contained in one of the case reports of Sir Charles

FIG. 2. The stele of Ruma. From the Ny Carlsberg Glypotek, Copenhagen.

Bell, the celebrated anatomist. He wrote in 1836, "A lady whose husband was an English clergyman at St. Helena consulted me about her child who had one leg much wasted in its growth. In conversing about the illness which preceded this affection in her little girl she mentioned that an epidemic spread among all the children on the island about three or five years of age and her child was ill of the same fever. It was afterwards discovered that

all the children who had the fever were similarly affected with a want of growth in some part of their body or limbs. This deserves to be inquired into."

It certainly did deserve to be inquired into. More than a century later the inquiry was more intensive, extensive and sustained than most inquiries into such occurrences. At that time the island of St. Helena was an important port of call for ships plying between South Africa and England. There is little doubt that poliomyelitis has been endemic in Africa since time immemorial. Only recently we were reminded that it still persists in Egypt.

Epidemic Patterns of Poliomyelitis

In the second World War, as in the first, poliomyelitis was more prevalent than in more normal times. Serious epidemics occurred successively and in turn affected many countries. The first of these affected the soldiers of the Australian and New Zealand Expeditionary Forces serving in the Middle East.[4] Malta then suffered its first severe epidemic.[5] It began in November, 1942, just after the relief from the prolonged siege. Then it was South Africa's turn.

Only three extensive epidemics of poliomyelitis have occurred in South Africa: the first, in the autumn of 1918, towards the end of the first World War, when South African soldiers were returning from the Middle East; the second in the summer of 1944–1945, when once again South African soldiers were returning from the Middle East. Soon afterwards, Mauritius and St. Helena Islands, on opposite sides of Southern Africa, experienced their most severe epidemics. The third epidemic occurred in the autumn of 1948. It was apparent that unusually invasive strains of the virus were abroad in the world. Conditions brought about by the war may have been responsible for their development, and certainly favored their spread. There are good reasons for suspecting that some of these strains originated in the Middle East. The large-scale troop movements created many opportunities for the widespread dissemination of virus diseases, especially those due to a relatively resistant virus such as that of poliomyelitis, which survives in and is excreted by its host for three weeks or longer. It seemed to us, therefore, that the strains responsible for the epidemics in South Africa in 1918 and 1944–1945 were introduced from outside the Union, probably from the Middle East.

In these epidemics it was noted that paralytic poliomyelitis was 10 times as frequent in the European as in the Bantu. It was also apparent that in the Bantu the majority of cases were in infants under five years of age. In the European there were as many cases in the 6–10 age group as in the 0–5 group.

These differences seemed to be of considerable significance. The possibility that the apparent relative insusceptibility of the African was due to inherent constitutional factors or to dietetic influences was considered. In

this regard it may be recalled that it has been found in this country and elsewhere that the Negro is much less susceptible than the European to benign tertiary malaria induced for therapeutic purposes. This resistance is not related to previous attacks of malaria, for it is shared by Negroes who have never been in a malarious region. Further, in South Africa, although syphilis is rife among them, the Bantu are less liable to tabes dorsalis and general paralysis than are the Europeans among whom syphilis is rare. Perhaps the central nervous system of the European is more vulnerable to this infection and to virus infections than is that of the Bantu.

It has been shown that diet influences the susceptibility of experimental animals to poliomyelitis. Thus mice fed on a diet deficient in thiamin are less susceptible to infection with the Lansing strain of virus than normal mice. The staple maize diet of the African, which is deficient in thiamin, may increase his resistance to poliomyelitis.

Interesting observations possibly having a bearing on this problem have recently been made by Dr. Anderson and Dr. Bersohn,[6] of our Institute. They have compared the serum proteins in the European and Bantu. In the Bantu the globulin-albumin ratio is considerably greater, due mainly to an increase in gamma globulin, the fraction associated with antibodies. These differences may be related to liver damage conditioned by the staple maize diet. They may also be an indication that the Bantu has a more efficient antibody-forming mechanism than the European. Such genetic and dietetic factors may determine or may help in determining the result of an infection in the younger age groups. However, the most likely explanation for the relative freedom from paralytic poliomyelitis of the older age groups of the Bantu appears to be that in their relatively primitive conditions they are early and regularly exposed to infection with endemic virus, and so they acquire an immunity not shared by the more advanced European.

The epidemics in South Africa conformed to a pattern which was to become familiar as the wave of infection swept round the world. Following the outbreaks in the Middle East in 1941, Malta was affected in 1942, South Africa in 1944, Mauritius and St. Helena Islands, on opposite sides of South Africa, in 1945, Northern Rhodesia in 1946, France in 1946, Britain and Germany in 1947, the Nicobar Islands in 1948, and South Africa again in 1948. During this time several severe epidemics occurred in the countries of the Western Hemisphere, which of course were no strangers to poliomyelitis.[7]

Studies of these epidemics have contributed in no small measure to the understanding of the epidemiology of the disease. Prior to the war, poliomyelitis was generally thought to be rare in tropical and subtropical countries. However, Paul, Havens and van Rooyen[8] observed that paralytic poliomyelitis was 10 times more prevalent in American soldiers in the Middle East than in American soldiers in the United States. Cases occurred among local children in Egypt, and, indeed, the number of cases in Egyptian infants

has subsequently been found to be much higher than was suspected at that time.[7] Severe paralytic infections resembling those observed in newly arrived Australian, New Zealand, American and European soldiers could not be duplicated in adult Egyptian civilians or soldiers. More recently, Paul [8] has analyzed the incidence of poliomyelitis in American troops in the various theaters of war. He found that the rates at which United States soldiers contracted poliomyelitis during the years 1943–48 were different in different parts of the world, and that these rates in the Far East and Philippine Islands were higher than elsewhere. As one explanation, he suggests that a large amount of poliomyelitis virus exists and persists in areas widespread throughout the world, whereas previously it had been the custom to consider it a rare disease.

The epidemiologic patterns of poliomyelitis in different parts of the world have been analyzed in detail by Sabin.[7] His data show that the risk of acquiring paralysis as a result of infection with the virus is not the same for all population groups in the same region or country, and varies markedly for people living in different parts of the world. In the greatly overcrowded and unhygienic communities of China, India, the Philippines and many other parts of the world, paralytic poliomyelitis was still relatively rare, sporadic rather than epidemic, and infantile when it did occur in the native population. The recent increased migration of adult Americans and British to these areas has brought forth not only many examples of continued adult susceptibility to paralytic poliomyelitis, but also evidence that the virus was present in abundance in those regions despite the rarity of the paralytic disease among the native children. While emphasizing the importance of genetic and constitutional factors in determining whether poliomyelitis infection shall result in paralysis, minor illness or inapparently acquired immunity, he notes that in general the poorer the population, its standard of living and sanitation, the more extensively is poliomyelitis virus disseminated among them and the lower is the incidence of paralytic poliomyelitis when virulent strains of virus come their way.

But primitive living conditions per se, within the tropics or elsewhere, are no guarantee of freedom from paralytic poliomyelitis. This was abundantly clear from the experience of the Nicobar Islands, whose primitive people in 1948 suffered one of the most severe outbreaks on record. In this epidemic, as in that which hit St. Helena in 1945, all age groups up to the age of 20 were equally and severely affected. Similar almost disastrous epidemics have occurred in the Arctic.

Genetic factors in these highly inbred populations may account to some extent for the exceptionally high paralytic attack rate. It seems, however, that in their isolation, whether in the tropics or within the Arctic Circle, these communities grew up out of contact with the virus, and so even the adults had no immunity when the virulent invasive strain responsible for the epidemic was introduced.

State of Immunity as Revealed by Serum Surveys

Considerable support for the theory that latent immunization is responsible for the relative immunity of many people and its lack for the greater susceptibility of others has been forthcoming from the results of serum surveys to determine the presence of antibodies to the poliomyelitis virus.

In one of the earliest of these, Paul and Trask [10] observed that the sera from persons from tropical countries contained a higher percentage of antibodies to the MV and Aycock strains than sera from the temperate zones. Hudson and Lennette,[11] in studying the incidence of poliocidal sera in regions where epidemics are infrequent, found that the sera of seven of nine adults on Thursday Island, off Australia, and 10 of 12 adults of Formosa (Brazil), possessed the property of neutralizing virus. They noted that in the former place sporadic cases of poliomyelitis occur, and that deaths from the disease had been reported from scattered parts of Brazil. These and similar findings suggest wide distribution of virus and disease and an associated generalized immunization.

Armstrong [12, 13] supplied an investigative tool of the highest importance when he adapted the Lansing strain of virus to cotton rats and then to white mice. The Lansing mouse protection test has supplied epidemiologic information which has done more than almost any other test to clarify the picture of poliomyelitis.

In their survey of immunity to the Lansing strain, Haas and Armstrong [14] found that the mouse protection test gave clear cut and consistent results, and that 68.7 per cent of the sera tested protected mice against the virus. The percentage of sera giving protection increased with the age of the donor, and had no relation to the individual's previous history of clinical poliomyelitis. More protection was shown by sera of persons living in orphanages than in private urban dwellings in the same age group, and more protection was shown by sera from Charleston, South Carolina, than by those from Detroit, Michigan. The suggestions inherent in the findings of these early surveys have been confirmed and amplified by subsequent studies.

In Baltimore, Turner and his colleagues [15] found that 72 per cent of infants under three months of age showed the presence of neutralizing antibodies to Lansing virus. Presumably these were passively transferred from their mothers. By one year of age the proportion with positive protection had declined to 10 per cent. The proportion with positive tests then rose as follows (figure 3):

Age	Per Cent
4	49
5–9	72
10–14	84
15+	89

The proportion of positive reactors was somewhat lower among white children in Baltimore than among Negro children. This they considered

probably a reflection of economic status rather than a difference due primarily to racial susceptibility. Repeated tests on 272 children who gave a negative neutralization test on initial examination showed that 51 became positive over a two year period, indicating a mean annual attack rate of 20.4 per cent. Observations of children initially negative over the summer and winter periods of two years showed that 40 of 201 became positive during summer, while only one of 224 children observed during the two comparable winter periods became positive. The data indicated that infections were largely acquired during the months of July, August and September. Among

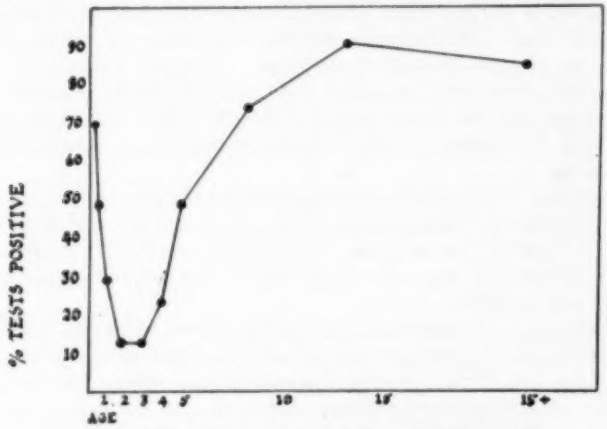


FIG. 3.

the children who presumably became infected during the observation period, not one developed signs suggestive of either paralytic or nonparalytic poliomyelitis. The incidence of minor illness was essentially the same as among children who did not develop positive neutralization tests. They concluded that Lansing poliomyelitis virus seems to be abundantly present in the population of Baltimore during the summer months, but the factors determining this striking seasonal distribution remain unexplained. Clinical poliomyelitis due to Lansing virus appears to be a rare development incident to infection.

Melnick and Ledinko [16] followed the rise and fall of several antibodies, including neutralizing antibodies to the Lansing strain, in a normal population during the course of an epidemic of poliomyelitis. The sera of 248 children, ranging in age from six months to 14 years, and 19 placental bloods, were tested for the following antibodies:

(a) Neutralizing antibodies to the Lansing strain of poliomyelitis virus.
(b) Neutralizing and complement-fixing antibodies to the local High Point Coxsackie virus.
(c) Antistreptolysin O agglutinins to heated Group A, type 4, hemolytic streptococci.
(d) Antihemagglutinins to influenza A virus.
(e) Antiagglutinins to Newcastle disease virus.
(f) Gamma-globulin content.

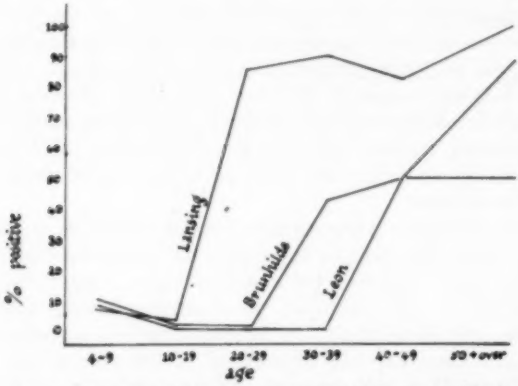
They noted that the children in Winston-Salem start life with a full complement of the antibodies studied. These antibodies drop to minimal level and, in most children, are no longer detectable at six months of age. With increasing age there is an increase in the over-all antibody development, but with each antibody developing at a specific rate. During the summer period the overall infection rate for Lansing type poliomyelitis virus was 17 per cent, and for the C virus 35 per cent. The other antibodies in the study did not change during the summer.

Turner and his colleagues regretted that it was not possible to draw firm conclusions from their data because there was no comparable information pertaining to the other types of poliomyelitis virus. Since then Paul, Riordan and Melnick [17] have published the most illuminating findings in their study of the state of immunity of the individuals of an isolated community in Alaska. These are best appreciated by reference to the accompanying chart (figure 4), which shows the level of antibodies found in different age groups of this community. Antibodies to the Lansing strain were found in high titer in individuals above the age of 20 years. These antibodies were presumably acquired by these Eskimos in 1930 or at some prior date, and had persisted for 20 years or more in the absence of reinfection. Antibodies to the Brunhilde and Leon strains were determined qualitatively and were found in an appreciable percentage of individuals over the age of 30 and 40 years, respectively. It seemed that these antibodies may also persist for 30 or 40 years in the absence of reinfection. This record of the appearance of Leon, Brunhilde and Lansing antibodies, as determined for the village of Barrow, suggests that exposure to these three strains occurred about 1905, 1915 and 1930, respectively, and that no such exposure has taken place since. Only one child below the age of 20 had antibodies to all three strains, and this child had probably visited outside the Arctic community. A few fatal cases of poliomyelitis were known to have occurred in 1930, and a medical missionary informed them of an epidemic prior to 1921, but its exact date was not clear.

Olitsky and Findlay [18] tested the sera of West Africans for antibodies against the M.E.F. I strain, a virus of the Lansing type. All of the 72 bloods tested neutralized the virus. The individuals from whom these bloods were collected included young children as well as adults. In our study it was

found that in all age groups a greater proportion of Bantu than of Europeans had Lansing antibodies.

As it seemed important to us to prove that the antibodies which appear at some time in the serum of most individuals were due to infection, a study of a group of Bantu babies was undertaken with the help of Dr. Faerber, of the Germiston Health Department.[19] These babies were tested at regular intervals for the presence of virus. Beginning within 14 days of birth, specimens of feces have been collected at monthly intervals and tested for the



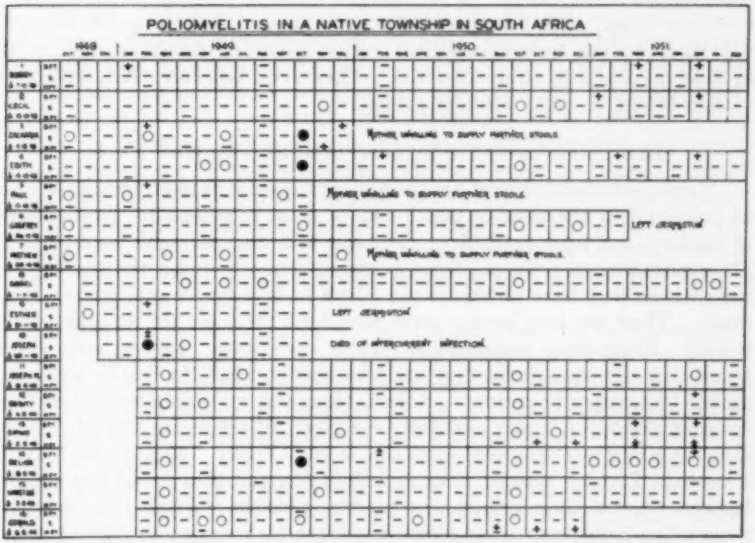
Comparative age distributional rates at which neutralising antibodies (determined qualitatively) for 3 strains of poliomyelitis virus (Lansing Brunhilde & Leon) appeared in the population of Barrow Village, Alaska. (After Paul et al)

FIG. 4.

presence of virus by the inoculation of an ether-treated suspension intraperitoneally into vervet monkeys. Of the 29 infants selected, 16 remained under observation for the first full year of this study. None showed any signs or symptoms suggestive of poliomyelitis. Four (25 per cent) of these 16 were proved to be infected with the virus of poliomyelitis during this time (figure 5). One contracted the infection in the third month, one in the eighth month and two in their twelfth month. The virus isolated from the infant in its third month proved not to be of the Lansing type. One of the other three was proved to be of the Lansing type and was successfully adapted to rodents. The remaining two were presumably also of the Lansing type. The infant infected with the non-Lansing virus did not subsequently develop antibodies against the Lansing strain. Two of the infants infected with the Lansing type of virus developed Lansing antibodies following their infection. This study confirmed that the Lansing antibodies demonstrable in the sera

of most older Bantu children develop as a result of a previous, usually silent infection with this type of virus. We found that such silent epidemics may also occur among older children.

In 1948 we collected specimens of feces from 12 children, between the ages of six and eight years, attending a school in a village in Swaziland, a native territory adjoining South Africa. The nearest paralytic case known to have occurred recently was over 20 miles away. These specimens were



B.P.T. = Result of Lansing mouse protection test on babys blood.
S = Result of test for poliomyelitis virus in stool.
M.P.T. = Result of Lansing mouse protection test on inoculated monkeys blood.
– Negative result of test for poliomyelitis virus.
● Positive result of test for poliomyelitis virus.
○ No specimen received for test.

FIG. 5.

collected to serve as controls for other tests. Suspensions from nine of them were inoculated into monkeys. Much to our surprise, three of the nine monkeys inoculated developed typical paralytic poliomyelitis. Sections of their spinal cords showed the characteristic lesions. None of these children had symptoms suggestive of poliomyelitis. These findings indicated clearly that a silent epidemic of infection with the virus of poliomyelitis was occurring in this school at the time of the collection of these specimens. Subsequent investigation proved that this virus was of the Lansing type.

Lansing Antibodies in Animals

Immunologic surveys of sera from various animals have revealed that some of them have neutralizing antibodies to the Lansing strain. Thus we have found such antibodies in the blood of cows, fowl, ducks and pigeons. Hammon and his colleagues [20] have found them in a variety of domestic animals, including cows, horses, cats, dogs, goats, sheep and chickens, but not in the sera from various wild animals. The significance of these interesting observations is not clear. An explanation for their presence in the blood of cows was found when Chang and Wenner [21] showed that calves, on recovering from bovine encephalomyelitis virus infection, developed antibodies against the Lansing strain of virus. They note, however, that these two viruses belong to quite different groups.

Immunity Revealed by Complement Fixation Tests

Virus neutralization tests are prodigal of the animals used, and in the case of poliomyelitis the number which can be done is limited by the numbers of monkeys and mice available. They also take a considerable time to complete, more time than the physician attending a puzzling case and seeking the information they have to impart can afford to give before making his diagnosis. There has long been a great need for a serologic test to detect antibodies. Many have attempted to devise such tests. Loring and others found that complement fixation could be observed but the results were obscured by nonspecific factors. Roberts described a flocculation test with a complex antigen. It was only last year that real success in the case of the Lansing strain was achieved, when Casals and Olitsky [22] adapted the M.E.F. I strain, a Lansing type of virus, to baby mice, and then found that the infectious titer of their tissues was greatly enhanced. From these infected tissues they have prepared an effective antigen for complement fixation tests. Lahelle [23] has prepared a similar antigen from baby cotton rat brains infected with the Lansing virus. The application of such a test will greatly facilitate many of the serologic studies, including the most interesting studies in social serology at present being undertaken in various parts of the world.

Factors Precipitating Paralysis

It is clear that of all those infected, even with the most virulent strains of virus, only a minority will develop any signs of illness and still fewer will develop paralysis. Why these few should be so unfortunate is a most important question. If it were not for the paralysis it causes, no one would worry much about the infections caused by the virus of poliomyelitis. Some of the factors are known; most remain to be unveiled. Undoubtedly the virulence of the virus is an important factor. The resistance of the host, apart from any question of previously acquired immunity, is probably of paramount importance.

Many years ago Draper [24] noted that paralytic cases of poliomyelitis had a characteristic appearance, having long eyelashes, wide apart eyes and separated incisor teeth. Most authorities doubt whether Draper's observations have been confirmed in other epidemics. It is a strange fact, however, that it is the best cared for children and the most attractive child of the family who seem to be specially prone to paralytic poliomyelitis.

For long it has been suspected that severe or prolonged exercise predisposes an infected individual to severe paralysis. Recently Ritchie Russell and Dorothy Horstmann [25, 26] have confirmed this suspicion. Ritchie Russell surmises that this probably explains why the child or individual who does not readily give in to feeling off-color is liable to severe forms of the disease. Our records show that long tiring journeys, either by plane, train, motor car, bicycle or on foot, also predispose infected individuals to paralytic poliomyelitis. Operations on the mucous membranes of the mouth and throat, including tooth extraction and tonsillectomy, should not be undertaken during an epidemic if they can be postponed without detriment to the patient's health. If a child should be harboring the virus at the time of operation, or should become infected within a month or two afterwards, he is more liable to the bulbar form of the disease than he would be if he had not recently undergone the operation.

There is now convincing evidence that the inoculation of certain vaccines increases the chances of paralysis in children infected with the virus within about one month of the inoculation. McCloskey,[27] in Melbourne, Australia, found that of 340 cases of poliomyelitis 31 had received an injection of diphtheria toxoid or pertussis vaccine alone or in combination within three months of the onset of symptoms. Bradford Hill and Knowelden,[28] after their investigation of the problem in England, concluded that their statistics reveal clearly an association between recent injections and paralysis. There are suspicions that other injections, such as penicillin injections, given during the primary wave of fever, may make the injected child and his injected limb more liable to paralysis than would otherwise have been the case. The matter needs statistical analysis to prove the association. In the meantime, one should perhaps hesitate during the poliomyelitis season before giving an injection to a child with a febrile illness for which no cause is apparent. Pregnancy also predisposes to a paralytic infection.

The tragic story of a family in Southern Rhodesia emphasizes some of the factors concerned in increasing the severity of poliomyelitis virus infections. The father was a medical missionary who had recently arrived with his wife and two children in Southern Rhodesia from England. The youngest child, who was teething, took ill and died of what at the time was thought to be cerebral malaria but was in fact bulbar poliomyelitis. Soon afterwards the mother, who was pregnant, became ill and developed paralysis. Meanwhile the other child, who while feeling off color had attended an exciting and strenuous party, became ill and developed paralysis. The

father felt ill and feverish but, in his own words, felt he "must keep going." Soon afterwards he also was admitted to hospital with bulbar paralysis, from which he died.

Duration of Immunity

The immunity conferred by infection is of long duration. The immunity induced by experimental infection in monkeys has been proved to last at least one year. The antibodies induced by the natural infection of our Bantu babies have lasted for two years in the absence of reinfection. That immunity may persist many years longer than this is clear from the serologic study of the Alaskan Eskimos of Barrow, reported by Paul and his colleagues.[17] Indeed, their findings suggest that immunity may persist a lifetime. The age pattern of paralytic cases confirms this view. It would not be an infantile disease if it were not so.

Second attacks of poliomyelitis are rare but not unknown. Bodian [29] has investigated several cases and has shown in one case that the virus responsible for the second attack was antigenically distinct from that causing the first attack.

Immunologic Types of Poliomyelitis Virus

The possibility of there being more than one type of poliomyelitis virus was not given much thought until 1931, when Burnet and MacNamara [30] showed that the virus isolated from a child in the epidemic in Victoria, Australia, was different from the Rockefeller mixed virus in both cross-immunity and neutralization tests in vitro. This suggestion was confirmed by Paul and Trask.[31] More recently, Bodian, Morgan and Howe [32] and Kessel and Pait [33] have shown in their independent studies of the antigenic relationships of 14 and 12 viruses, respectively, that there are at least three basic immunologic types. A comprehensive study was then planned and undertaken by the Typing Committee of the National Foundation for Infantile Paralysis.

Three methods of typing were used:

(1) Testing resistance to unknown strains in monkeys vaccinated and immune to the prototype virus.
(2) Neutralization of unknown strains with prototype antisera.
(3) Neutralization of prototype viruses with antiserum for unknown strains.

The typing of the first hundred strains confirmed that they all belonged to one of three types, namely:

Type Name	Number Found in First 100
Type 1 Brunhilde virus, Baltimore, Maryland, 1939	85
Type 2 Lansing virus, Lansing, Michigan, 1938	12
Type 3 Leon virus, Los Angeles, California, 1937	3

The extension of these studies will be watched with interest, particularly to see whether further types are unearthed. They will be watched with particular interest at the present time, for the main conclusion to be drawn from these studies is that paralytic poliomyelitis would be a rare disease if the high degree of naturally acquired immunity enjoyed by most people living in primitive surroundings could be artificially produced. Obviously we cannot advocate a return to their primitive ways. The question naturally follows, can those at risk be immunized?

Prevention of Poliomyelitis

Passive Immunization: Convalescent and adult serum in the prophylaxis and treatment of poliomyelitis has been tried and found wanting. The whole subject, however, needs re-assessment in the light of the recent advances in our knowledge of the types of poliomyelitis virus and of the value of more concentrated preparations of antibody, such as refined and concentrated gamma globulin at present available. There is no doubt about the value of these preparations in the prophylaxis of measles; Bodian [35] has shown that a sample of gamma globulin refined and concentrated about twenty-three fold from pooled adult human plasma has high neutralizing antibodies against the three distinct antigenic types of poliomyelitis virus—Brunhilde, Lansing and Leon. Hammon [34] has been particularly impressed by the possibility of passive immunization with gamma globulin. He notes that it might not prevent infection, but should prevent clinical disease. It thus would not prevent the development of permanent immunity through inapparent infection. Its use would be recommended only during epidemic years and for only the more susceptible age groups. Perhaps the recent trials of gamma globulin will provide an answer to the question of its value in the mass prophylaxis of poliomyelitis. If found to be of preventive value, however, it still is not the best method of prevention, mainly because it confers a passive immunity which does not last. For many reasons an active immunity is more desirable.

Active Immunization: For many years now, intensive efforts have been made to develop prophylactic vaccines. Broadly, these have been of two types. The first have consisted of living, presumably avirulent virus. Theoretically, living vaccines should confer solid immunity of long duration. Unfortunately they have not always proved avirulent.

Vaccines prepared from killed or inactivated virus theoretically would not confer such solid or long-lasting immunity. However, they are safe. Morgan [36] has shown that it is possible to immunize monkeys with formalin-inactivated virus against a severe intracerebral challenge of virulent virus.

Studies by Schwerdt and Dick and their colleagues [37] have demonstrated that it is possible to protect cotton rats against an intracerebral challenge of Lansing virus by vaccinating them with virus inactivated by formalin and by ultraviolet or ultrashort high intensity electron beam irradiation.

These early vaccines were produced from infected monkey cord or from the central nervous system tissue of infected rodents. There was no prospect of the large-scale production necessary to immunize all those needing protection. The question may well be asked, what are the chances of producing large amounts of a vaccine effective in conferring immunity against poliomyelitis?

Here we can turn for encouragement to the story of yellow fever, which shows many parallels with the story of poliomyelitis that are worth noting. In yellow fever, as in poliomyelitis, the virus was first transmitted to monkeys. Then Max Theiler found that the white mouse could be infected experimentally by intracerebral inoculation, and so laid the foundation on which much of our knowledge of the extent and epidemiology of yellow fever was built. The first effective yellow fever vaccine was prepared from this neurotropic, mouse-adapted virus. Similarly, the work made possible by Armstrong's discovery of the susceptibility of white mice to the Lansing strain of virus has greatly extended our knowledge of the epidemiology of poliomyelitis. Infant mice were found very sensitive to the yellow fever virus. Their use in the field of poliomyelitis led to the unveiling of the Coxsackie group of viruses and also to the development of an effective antigen for complement fixation test.

Theiler [38] found that after several rapid passages in mice the Lansing strain became relatively avirulent for rhesus monkeys. We tried out the effect of rapidly passaging the Lansing virus through *Mystromys irrorattus,* one of the common rodents of the South African veld. It breeds well in captivity, and adequate numbers were available for this experiment. The fortieth passage virus was tested for virulence in monkeys. Of the seven monkeys inoculated intracerebrally, two developed paralysis and showed the typical lesions of poliomyelitis in sections of the spinal cord and brain. The five surviving monkeys showed no signs of illness but subsequently were proved to have developed Lansing antibodies. The hundredth passage virus was inoculated into 10 monkeys. One developed paralysis and showed the lesions of poliomyelitis in the spinal cord. The other nine remained well, and eight of them developed Lansing antibodies. Of 10 monkeys inoculated with the original strain, nine developed severe paralysis. Some attenuation of the virus as a result of its passage through *Mystromys* was apparent. We wondered whether it would be safe to administer this attenuated virus orally to human beings, and whether such human beings would develop immunity as a result. We did not try, although we considered that little untoward would happen. However, Koprowski and his colleagues [39] had the courage we lacked: they fed 20 human volunteers with living TN poliomyelitis virus. This strain was found to have a low pathogenicity for rhesus monkeys, even on intracerebral inoculation. Following oral administration of the virus, most of the volunteers manifested a carrier state, as demonstrated by excretion of virus in their stools. None of them

suffered any signs or symptoms of illness. All of the nonimmune volunteers promptly developed antibodies in their blood.

Such avirulent strains of virus may well provide the answer to the problem of immunization against the Lansing strain of virus. Unfortunately they do not immunize against the non-Lansing types, and therefore do not provide an answer to the problem of epidemic poliomyelitis, as most epidemics appear to be caused by non-Lansing types of virus.

In the case of yellow fever the development of a safe living avirulent vaccine, capable of large-scale production, followed on the adaptation of the virus to tissue culture by Theiler and his co-workers.[40] After many earlier disappointments, culture of poliomyelitis virus in nonnervous human tissue has at last been successfully achieved by Enders and his colleagues. To many this appears to be the most important and promising advance made in recent times. Indeed, it marks the beginning of a new era, when great advances can be expected.

If the parallel with yellow fever continues, avirulent strains of virus will be developed which could be used in a vaccine to confer immunity against poliomyelitis. It can be confidently forecast that large amounts of virus, produced from either human or monkey tissue cultures, will become available, and that there will be no difficulty in including all of the three known types of poliomyelitis virus in a vaccine. The next question that arises, and one which will have to be fully debated very soon, is, What are the potential dangers of such vaccines? In the now long history of vaccines there have been several tragic accidents from their use. Will vaccines against poliomyelitis be free from such dangers? Here it will have to be decided whether a living vaccine is safe, and, if not, whether an inactivated vaccine is effective, and, if effective, what is the best method of inactivation. Attention is now being paid to these problems. Of course, the avirulence of the virus will be fully established before the general use of a living vaccine is advocated, but again the experience with yellow fever comes to mind. This is the most effective human vaccine so far evolved. It was apparently free from all danger, and actually the 17-D strain of yellow fever virus has proved to be exceptionally free from bad traits. But it was noted, first by Findlay and McCallum [41] and then by workers of the International Health Division of the Rockefeller Foundation,[42] that a considerable proportion of the individuals vaccinated with certain batches of vaccine developed jaundice. This was later proved to be homologous serum jaundice, related to the human serum content of the vaccine and not to the virus. Virus vaccines produced in tissue culture of human cells will also have this potential danger, and it is not clear whether the responsible agent is inactivated by the usual concentration of formalin.

There is no record of homologous serum jaundice following the injection of monkey serum into human beings, but many diseases of man are transmissible to monkeys. Presumably the converse is true, but our knowledge is

fragmentary. On record are two cases of human laboratory infection with virus B, one following a monkey bite, the other following contamination of abrasions with monkey saliva. Until proved to be free, monkey tissues will have to be suspected of this infection. Virus B is closely related to herpes virus, and is readily inactivated by formalin, and therefore would not be a danger in formalinized-killed vaccines.

These are probably minor hazards, but they should be eliminated. Oral administration may provide the answer to the problem. This method has already been shown by Koprowski [39] and his colleagues to be effective in stimulating antibodies. If given in jam or syrup it would be no hardship to a child to take the virus.

To many it may seem premature to be discussing these matters, but the situation in poliomyelitis is brighter now than it has ever been. The dawn of a new day has come, the day when it will be possible to prevent paralytic poliomyelitis. For the dawning of this day we have to thank the workers in this country, and the National Foundation of Infantile Paralysis, which has sustained their efforts. Indeed, the attack on poliomyelitis planned and coördinated by the National Foundation for Infantile Paralysis is now making notable advances on all fronts. We seem to be on the eve of a triumph in preventive medicine which would have gladdened the heart of James Deacon Bruce, whose memory we honor in this lecture.

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INDICATIONS AND CONTRAINDICATIONS FOR TREATMENT OF THYROID CANCER WITH RADIOACTIVE IODINE*

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TEN years have now elapsed since the first patient with carcinoma of the thyroid was treated with radioactive iodine.[1] More than 250 thyroid carcinoma patients have been treated since then with radioactive iodine, I^{131}.[2] Review of the literature and our experience in treating 24 such patients have indicated certain criteria to be of definite value in the selection of patients for I^{131} therapy. Lack of regard for these criteria has, in our hands, led to wasteful use of I^{131} and rise of false hopes in the thyroid cancer patient. It is the purpose of this discussion, therefore, to review these indications and contraindications.

1. *Previous Thyroidectomy:* Total thyroidectomy, with radical neck gland dissection when indicated and possible, is the most effective method of treating thyroid cancer today. No patient with thyroid cancer should be deprived of this most effective and proved form of therapy for the sake of an experimental trial of radioactive iodine therapy. Surgical removal of the neoplastic thyroid gland usually prevents death from compression or invasion of the trachea, the esophagus or the superior vena cava. Total thyroidectomy in such cases also removes normal thyroid tissue. If functioning thyroid is not removed, its hormone continues to check the pituitary's production of thyroid stimulating hormone, TSH (figure 1). When this source of thyroid hormone is removed, on the other hand, the pituitary's increased secretion of TSH tends to increase the capacity of metastatic thyroid cancer to pick up radioactive iodine.[3] In summary, then, radioactive iodine is not indicated unless the patient has first had a total surgical thyroidectomy, in order, first, to prevent death from local growth of the primary tumor, and, second, to encourage the pituitary to stimulate metastases to a greater affinity for radioactive iodine.

2. *Previous X-Ray Therapy:* X-ray therapy is a proved adjunct to surgery in the treatment of thyroid cancer. The patient's life will be risked needlessly by a trial of radioactive iodine therapy if x-ray therapy is not tried first when the surgeon is unable to eradicate all palpable or visible neoplasm. Sometimes the x-ray therapist refuses the patient for treatment because the

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From the Department of Internal Medicine, University of Michigan Medical School. The radioactive iodine used in this investigation was supplied by the Oak Ridge National Laboratories, Oak Ridge, Tennessee, and was obtained under allocation from the United States Atomic Energy Commission. These studies were assisted by a grant from the Michigan Memorial Phoenix Project, University of Michigan.

metastases are too widely disseminated or because previous roentgen therapy has been ineffective.

After these two well established forms of therapy have been adequately employed, the presence of remaining neoplasm or recurrences warrants consideration of the use of radioactive iodine. What procedures will yield information as to whether this patient will enjoy a good response to treatment with radioactive iodine?

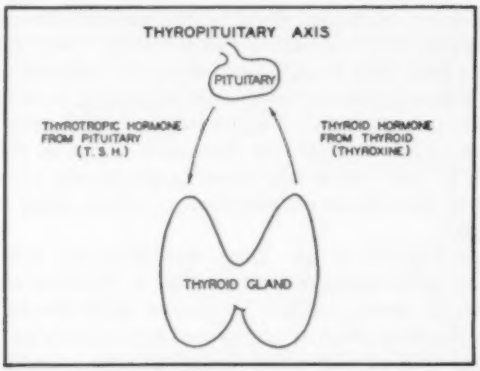

FIG. 1. If total thyroidectomy is first performed, the check is taken off the production by the pituitary of thyrotropic or thyroid stimulating hormone so that its stimulation of functioning thyroid cancer to pick up more radioactive iodine is enhanced.

3. *Biopsy:* Previous surgery has already supplied biopsy material. The normal thyroid concentrates iodine from the circulating blood. Cancerous thyroid must resemble normal thyroid enough to pick up radioactive iodine if good results are to be achieved by treatment with this isotope. Review of the literature reveals that follicular and alveolar carcinomas most commonly show good response, papillary carcinomas less commonly.[4a, b] Good therapeutic response in more undifferentiated thyroid carcinomas has not been reported. Undifferentiated carcinoma of the thyroid, then, is a contraindication to radioactive iodine therapy.

When possible, one or more of the metastases should also be biopsied. If many of the metastases are quite undifferentiated, it is useless to try to cure the patient with radioactive iodine even when the primary lesion had shown follicular and alveolar structure. No statistically significant figures are available to tell us what percentage of the patients with fairly well differentiated primary lesions have undifferentiated metastases. The four patients in our series enjoying an unequivocally good response were demonstrated to have the same type of pathology in both primary and metastatic processes (figure 2).

4. *Demonstrated Ability of Neoplasm to Concentrate I^{131}:* If biopsy reveals a picture to the pathologist compatible with a good response to I^{131},

attempts to demonstrate ability of the neoplasm to concentrate iodine will further indicate whether the patient is a good candidate for I^{131} therapy. Four methods are commonly used to test the ability of the neoplasm to concentrate iodine: autoradiography, external gamma counting, urinary excretion of I^{131}, and I^{131} level in the circulating blood.

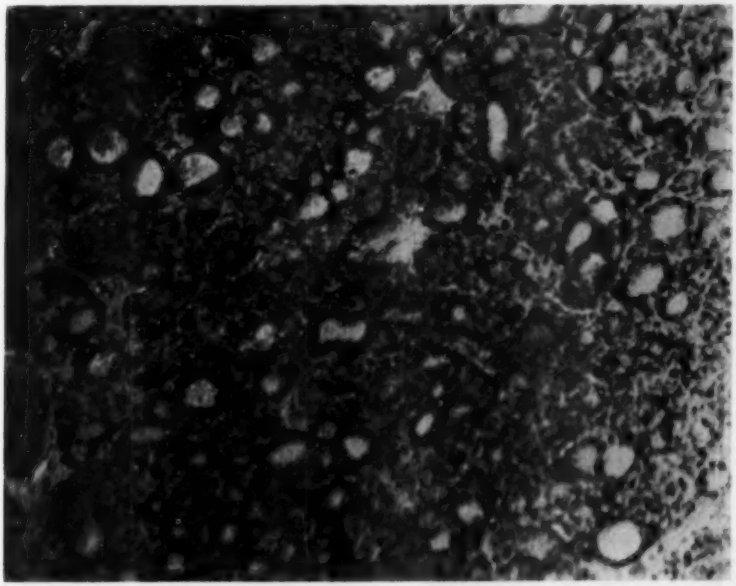

FIG. 2. F. F.—Biopsy of ileal metastasis from 61 year old woman, showing follicular and alveolar type thyroid carcinoma identical in morphology to the primary neoplasm in the thyroid gland. (Courtesy Dr. C. V. Weller, Chairman, Department of Pathology.)

When a tracer dose of radioactive iodine is administered to a patient having cancer of the thyroid with metastases, a subsequent biopsy slice of the cancer tissue exposed to photosensitive film will produce an image of the tissue if the tissue has picked up enough radioactive material to expose the film. This technic is called autoradiography (figure 3).

External counting of gamma emissions over an area of known metastasis and comparison of this count with the count over a similar anatomic area give an approximation of the amount of I^{131} taken up by that metastasis. Relatively small metastases near the body surface showing an uptake count in 100 seconds that is greater than 15 times the count over a similar anatomic area usually show retrogression on exposure to a treatment dose of I^{131} (figure 4). Most authors utilize this technic regularly because of its simplicity.

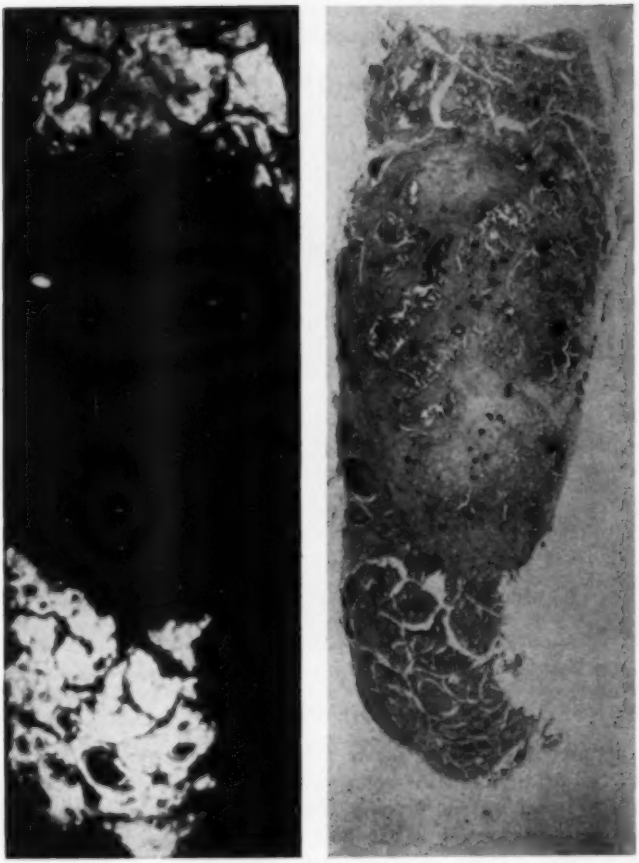

FIG. 3. Autoradiogram above and control tissue section below, showing uptake of radioactive iodine in normal thyroid tissue at each end of an area of undifferentiated thyroid carcinoma. This 17 year old boy was treated unsuccessfully with radioactive iodine later, but responded to x-ray therapy.

It is thought that one of the most accurate methods of predicting a good therapeutic response to I^{131} in a given patient with carcinoma of the thyroid is excretion in the urine of preferably less than 30 per cent of a tracer or therapeutic dose of I^{131} in the first 48 to 96 hours after administration of the dose.[5] The value of this test is lessened, however, by the fact that a patient with one metastasis weighing only a few grams might "trap" relatively little I^{131} for this period, compared to another patient with 1,000 gm. of metastases that were gram-for-gram equally active in concentrating I^{131}.

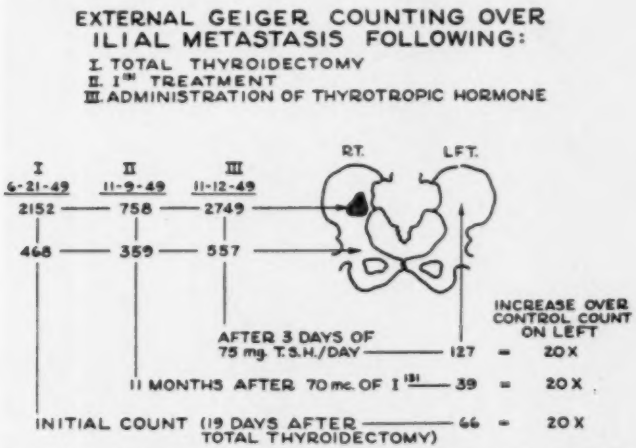

FIG. 4. F. F.—External Geiger counting over area of metastasis in wing of right ileum (pathology seen in figure 2), showing twentyfold uptake of radioactive iodine in metastasis 24 hours after administration of 1 mc. tracer dose orally. Sixty per cent of this tracer dose was excreted in the urine during the first 72 hours.

The blood radioiodine level after a tracer or treatment dose has been used much like the urinary iodine excretion test. The presumption is that the more I^{131} concentrated by the thyroid, the less available to the circulating blood. Here again, however, differing volumes of functioning metastases and their rate of iodine turnover render this index less valid.

When the patient with metastatic thyroid neoplasm has been evaluated by these criteria and found worthy of further consideration for radioactive iodine treatment, it then will be advantageous to enhance I^{131} uptake by one or more of several different methods of increasing the stimulation of metastases by TSH. Thyroidectomy is the first and most helpful method.[2] We have already discussed this physiologic effect of thyroidectomy. It should be emphasized that academic enhancement of I^{131} uptake is not enough. One author reported that, although 21 out of 35 patients subjected to total thyroidectomy developed a significantly increased function of metastases, only two of these showed enough increased avidity for I^{131} to justify administra-

tion of the isotope in therapeutic amounts.[4a] Another report showed uptake of I^{131} initiated by thyroidectomy in six and increased in nine out of 18 follicular and papillary carcinomas.[4b] Even here, however, only three of 50 patients treated were noted to have unequivocal decrease of bone, lung or cervical node metastases. No patients with more undifferentiated metastases showed increased uptake after thyroidectomy. Thiouracil and its derivatives produce the same response as surgical thyroidectomy, but are

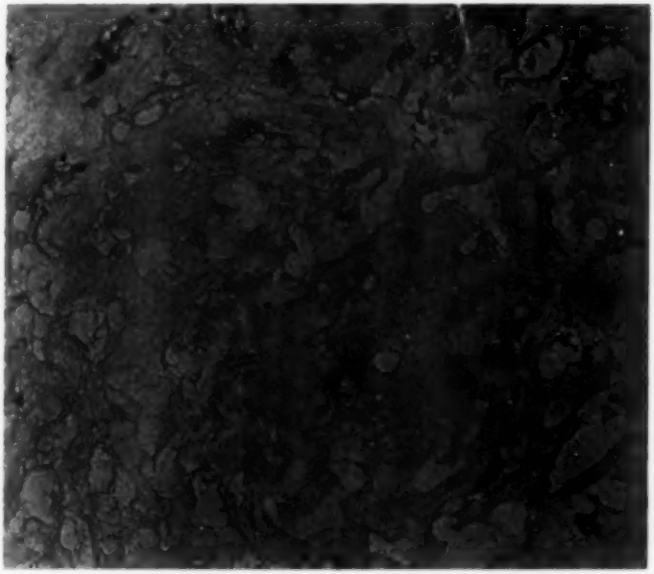

FIG. 5. F. F.—Repeat biopsy of ileal metastasis after one year and a total of 170 mc. of I^{131}. Little thyroid tissue is observed, and repeat roentgenograms of the pelvis showed definite evidence of bone regeneration, yet no symptoms, signs or laboratory evidence of myxedema were present. (Courtesy of Dr. C. V. Weller, Chairman, Department of Pathology.)

most effective after total surgical thyroidectomy if given for two months or longer and then stopped for two days before I^{131} is administered.[4a] The uptake will not be enhanced if the antithyroid drug is stopped two weeks before thiouracil is administered. Thyroid-stimulating hormone is commercially unavailable at present, and has varied greatly in potency when available in the past. It has been reported to increase the uptake as much as fourfold,[5] but is not so effective as thiouracil (figure 4).

Three temporary contraindications to I^{131} therapy may arise during this form of treatment. These are myxedema, desiccated thyroid or iodide administration, and hypoplastic marrow. Only a few grams of functioning

thyroid tissue need be present in the body to prevent the development of clinical outspoken myxedema (figure 5). Consequently, a patient with thyroid metastases who becomes totally myxedematous under treatment will rarely, if ever, show further significant response to treatment if I^{131} therapy is continuously pursued. No patient should be treated while on desiccated thyroid or stable iodine therapy, since their administration inhibits the uptake of iodine by functioning thyroid tissue.[6] The patient made myxedematous and then maintained on thyroid therapy should have future uptake studies performed only after desiccated thyroid has been stopped for a minimal period of six weeks.[7]

Patients with hypoplastic anemia or marrow made hypoplastic by radiation should have no further I^{131} treatment until clinical evidence of adequate cellular regeneration is present. If this policy is not followed, the patient may die of sepsis or hemorrhage while one is trying to cure him of cancer.

Summary

Review of the literature covering the first 10 years of I^{131} treatment of thyroid neoplasm and review of our cases treated since 1946 have revealed certain criteria to be of definite value in the selection of patients for I^{131} therapy. To be a suitable candidate for radioactive iodine therapy a patient first should have had a total thyroidectomy, with radical neck dissection when indicated. If the surgeon is unable to eradicate all palpable or visible neoplasm, the x-ray therapist should be given a chance to try for cure or palliation if he feels that this mode of therapy might help. When these well established forms of therapy have been used or deemed no longer helpful, biopsy will suggest that the patient is a good candidate for I^{131} therapy if it demonstrates follicular and alveolar or papillary neoplasm in primary and metastases. Another indication predicting a good response to therapy is demonstrated ability of thyroid cancer to concentrate I^{131} as shown by (1) a positive autoradiograph; (2) a high uptake in the metastasis demonstrated by external gamma counting; (3) less than 30 per cent of an administered dose of I^{131} excreted in the urine in the first 48 to 96 hours after the dose, or (4) low level of I^{131} in the circulating blood after a tracer dose of I^{131}. A more nearly complete response can be promoted by increasing the TSH effect on metastases through total thyroidectomy, thiouracil administration and exogenous administration of TSH.

Temporary contraindications to I^{131} therapy include clinical myxedema, administration of desiccated thyroid or iodides, and the presence of hypoplasia of bone marrow.

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THE TREATMENT OF SYSTEMIC BLASTOMYCOSIS WITH STILBAMIDINE *

By EMANUEL B. SCHOENBACH, M.D., F.A.C.P., *New York, N. Y.*, JOSEPH M. MILLER, M.D., *Fort Howard, Maryland,* and PERRIN H. LONG, M.D., *New York, N. Y.*

ALTHOUGH infrequent in occurrence, blastomycotic infections are important because of the morbidity and mortality associated with the systemic form of the disease. Treatment has been varied and generally ineffectual. The observation of Elson [7] that certain of the diamidines exerted a fungistatic effect on *Blastomyces dermatitidis* led to the treatment of a patient suffering from systemic blastomycosis with two of the diamidines.

Blastomycosis is seen in both the white and Negro races, usually in the third through the fifth decades of life and in the lower economic strata. The incidence is much higher in males. Farmers are more frequently affected than any other workers.[8]

Martin and Smith,[21] in reviewing 347 cases of blastomycosis, reported that 80 were unquestionably due to *Blastomyces dermatitidis,* that the diagnosis was presumptive among 163, and that confirmatory data were inadequate for diagnosis in the remaining 104. The sex and age incidence corresponded to the statistics reported by Friedman and Signorelli.[8] Of the 243 cases classified as proved or presumptive by Martin and Smith,[21] 50 per cent had initial respiratory symptoms. Among 4 per cent the primary lesion followed some type of injury. A superficial skin lesion was first noted in 19 per cent, and in 23 per cent a subcutaneous nodule or abscess was the initial manifestation. Any organ in the body can be involved in blastomycotic infection, but the sites of predilection are the skin and subcutaneous tissues, the lungs, the bones or joints and, less commonly, the central nervous system. The gross mortality for proved and presumptive cases was 78 per cent. If the patients upon whom follow-up observations were lacking are excluded, the mortality rate was 83 per cent. The exclusion of patients who were followed for less than two years from the series would change the mortality rate to 92 per cent.

Martin and Smith,[22] on the basis of this survey plus their experience with 13 patients in their own series, recognized two types of infection with blasto-

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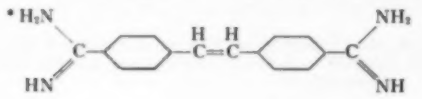
myces: (1) *The Cutaneous Type.* This proceeded as a chronic or subacute ulcerating process and usually responded to iodides or radiation. (2) *The Systemic Type.* This was a highly fatal disease characterized by pulmonary infection and widespread distribution of lesions in the subcutaneous tissues, bones, joints, central nervous system and other viscera. These authors concluded that potassium iodide was curative in some cases but was dangerous to patients allergic to the fungus. They advised that in systemic disease potassium iodide be employed only after hypersensitiveness had been excluded by skin test or reduced by therapeutic injections of a vaccine.

Martin and Jones [20] reported that the treatment of blastomycosis varied with the individual, depending upon the extent of the infection, the degree of allergy developed by the patient and the anatomic location and the nature of the individual lesions. They reëmphasized the observation that iodides were potentially harmful to patients who had developed a high degree of sensitivity, and concluded that those patients without evidence of hypersensitivity appeared to respond well to iodides.

In reviewing reports of generalized blastomycosis, Jones and Martin [17] found 63 patients with bone involvement, of whom seven recovered after treatment and 53 died. The outcome was unknown for three patients who were not followed. The authors suggested that patients with bone lesions be desensitized with blastomycosis vaccine before initiating either iodide or surgical therapy.

In general, treatment has been unsatisfactory. Iodides, desensitization with vaccine followed by iodides,[8, 22] arsphenamine followed by iodides, cauterization, excision and radiation [8] have been suggested. Penicillin therapy has not been beneficial,[8] and a combination of streptomycin and penicillin [19] was also ineffective in treating blastomycosis. Only a single preliminary report [27] is available in which an immediate therapeutic effect of stilbamidine and propamidine in the treatment of advanced generalized North American blastomycosis was observed. These observations have since been extended. The properties and clinical effects of the aromatic diamidines are briefly reviewed to familiarize the physician and surgeon with these potentially valuable agents.

Stilbamidine (4.4′ stilbenedicarboxamidine) * is a white crystalline powder which is stable in the dark. The compound is soluble in water up to 40 gm. in 100 c.c. at 25° C. It is fairly soluble in glucose solutions and moderately soluble in the usual blood citrate mixtures.[26] Fulton and Goodwin [10] have demonstrated that the addition of stilbamidine to human serum in concentrations greater than 0.5 per cent results in precipitation as the base.



Solutions of stilbamidine are markedly affected by even short exposure to light,[2, 9, 11, 18] whereas similar solutions kept in total darkness over a period of months remain unaffected. Fulton [9] found a sixfold increase in toxicity of the solution after exposure to light for two days. Changes were also demonstrated after an exposure of one-half hour to winter sunlight, with a significant loss in therapeutic properties. Fulton [9] suggested that the deterioration was due to the saturation of the ethylenic linkage. Barber, Slack and Wien [2] reported a four- to fivefold increase in toxicity of 0.5 per cent solutions of stilbamidine exposed to sunlight. The process of deterioration continued for four days, after which little change was noted. These authors believed that the reaction probably consisted of the addition of water to the double bond of the stilbene linkage and the formation of 4,4′ diamidinophenyl-benzyl-carbinol. Henry,[12, 14, 15] however, reported that old solutions contained a mixture of substances, and that sunlight acted by accelerating a process of cis-trans isomerization with the unstable amidine groups being converted to amido groups. Stilbamidine possesses a brilliant blue fluorescence even in dilute solutions when exposed to ultraviolet light.[16] The cis isomer does not fluoresce.

Because of the remarkable absorptive properties of stilbamidine to filter paper and its fluorescence, it is possible to detect its presence in dilutions as great as one part in two million. The body fluid to be studied is spotted on filter paper, exposed to ultraviolet light, and the characteristic fluorescence observed. The method is only qualitative, as a considerable margin of error exists at the low concentrations of stilbamidine encountered physiologically. In spite of numerous modifications, only those blood levels obtained in man immediately after maximal tolerated doses administered intravenously can be measured with reasonable accuracy.

Within a few minutes of administration, stilbamidine may be detected in relatively high concentrations in the blood or urine of man or various experimental animals.[10, 16, 25] Peak levels of the drug are maintained for only a short time. The reason for the rapid disappearance of the stilbamidine from the blood is not known, but the remarkable absorptive qualities of the compound have been suggested as responsible for its rapid disappearance. The drug is stored in the liver for long periods of time.[23]

Observations indicate that stilbamidine, in therapeutic dosage, would not be expected to produce clinical evidence of hepatic or renal damage unless such damage was present before treatment was started. Devine,[6] studying the effect of graded doses of stilbamidine in rabbits, found that a single intravenous injection of half the lethal dose, 15 mg./kg., did not cause any significant change in the blood glucose level, although the blood urea rose from 35 mg. per cent to over 100 mg. per cent. Single intravenous injections of 25 mg./kg. produced immediate vascular collapse, followed by prompt recovery within an hour. Within two hours a transient rise of almost 100 per cent occurred in the blood sugar concentration, which was followed by a

rapid fall to normal. Hypoglycemia did not follow the hyperglycemia. The animals, however, showed evidence of prolonged impairment of renal function with either transient or fatal uremia. Some animals died after eight to 10 days. Six daily injections of 5 mg./kg. did not produce changes in the chemical constituents in the blood.

Similar results were obtained by Wien, Freeman and Scotcher [36] when studying phenamidine (p,p′ oxydibenzamidine), stilbamidine (4,4′ stilbenedicarboxamidine), propamidine (p,p′—(trimethylenedioxy) dibenzamidine) and pentamidine 4,4′—[pentamethylenedioxy] dibenzamidine). Blood sugar levels were affected only when doses approaching a toxic level were attained. Adrenalin hyperglycemia was reduced by previous injection of stilbamidine. Repeated injections of stilbamidine depleted the liver of glycogen, which, however, was probably due to the accompanying anorexia. The blood urea nitrogen and the non-protein nitrogen were increased. In dogs and rabbits, calcium and potassium levels were reduced in a few hours. The white blood cell count and the proportion of polymorphonuclear neutrophilic leukocytes were increased in the blood of guinea pigs preceding death when toxic doses were given. A fatty degeneration of the liver and cloudy swelling of the kidneys were also found in lethally poisoned animals.

Seager and Castelnuovo [28, 29] have reported upon the acute and chronic toxicity of stilbamidine. Mice given 100 mg./kg. orally daily for 120 days showed fatty metamorphosis of the liver and, in some instances, marked degeneration of the renal convoluted tubules. Evidence of damage in other organs was not found. Cloudy swelling and slight tubular degeneration in the kidneys were found in mice receiving 10 mg./kg. daily for one week. In the liver, distention of the central veins, the sinusoids and often the interlobular veins was a constant feature. Rabbits given 50 mg./kg. subcutaneously daily died in from one to 10 days. A loss of appetite and weight, weakness and sometimes diarrhea were noted in these animals. Ten mg./kg. daily killed all rabbits before 10 doses were given, while 100 mg./kg. produced convulsions and death in a few days. The symptoms were ascribed to a fall in blood pressure. Rabbits given 25 mg./kg. once a week survived for from four to five weeks. A fatty metamorphosis of the liver and extensive tubular degeneration of the liver were found.

Evidence of hepatic or renal toxicity following treatment in man has not been observed. Arai and Snapper [1] reported that repeated injections of freshly dissolved stilbamidine did not have delayed toxic effects upon the liver or the hematopoietic system of patients with multiple myeloma. Renal insufficiency, when present, was attributed to an exacerbation of preëxisting involvement caused by multiple myeloma or other disease. Stilbamidine could be administered to patients with renal failure not more than two to three times a week.[1]

Wien [34] has demonstrated that the administration of stilbamidine may be associated with a fall in blood pressure due to vasodilatation, as shown by

studies in the rabbit, rat and dog. The depressant action on the circulatory system was only partially antagonized by atropine. Kirk and Henry [18] point out that the immediate toxic reactions of stilbamidine may include a fall in blood pressure, generalized formication, sweating, breathlessness, dizziness, nausea, epigastric discomfort and vomiting. These symptoms were all transient. Salivation, incontinence of feces and urine and a puffy sensation of the face and eyelids were also noted. Kirk and Henry [18] advised that stilbamidine never be used for ambulatory treatment. Haedicke and Greenspan [12] reported that stilbamidine could be given by a slow intravenous drip without signs of immediate toxicity.

The late chronic toxicity of stilbamidine has been confined to a unique neuropathy. Two to five months after a course of stilbamidine, progressive sensory changes of paresthesia, anesthesia, hypalgesia and numbness, usually confined to the face, were observed.[1, 4, 5, 28, 31] Napier and Sen Gupta [28] found a subjective disturbance of sensation over various distributions of the trigeminal area. These included paresthesia, formication, hyperesthesia and anesthesia. Loss of sensation to light touch over this area was associated with the preservation of the sense of pressure and pain to produce a dissociated anesthesia. They suggested that the lesion was in the chief sensory nucleus of the trigeminal nerve in the pons. Among their seven patients the symptoms appeared three to four months after treatment for kala-azar. Sen Gupta [31] later reported an incidence of 17 patients with neuropathy among 104 with kala-azar who were treated.

Collard and Nevin [5] considered the lesion to be in the nucleus of the fifth nerve and in the central gray matter of the cervical part of the spinal cord. The nuclei affected were the chief pontine nucleus and the descending nucleus. They inferred that the stilbamidine was fixed by these cells and that functional abnormalities appeared after a long latent period.

Arai and Snapper [1] observed the neuropathy in 10 of 18 patients with multiple myeloma treated with stilbamidine. Collard and Hargreaves [4] reported a neuropathy in 22 of 24 patients treated with stilbamidine. Some of the cases in the latter series showed neuropathy extending to the chest and waist.

The mechanism of stilbamidine neuropathy is totally obscure. Oastler and Fidler [28] administered fresh solutions of stilbamidine to 10 dogs. Evidence of macroscopic as well as microscopic damage in the brain was found at postmortem examination. In the five dogs in whom clinical evidence of damage was not observed microscopic examination still showed alterations of the brain.

A local thrombophlebitis is frequently seen after the administration of concentrated solutions intravenously.[24] Propamidine, one of the aromatic diamidines, produced necrosis and an intense cellular reaction when injected intramuscularly in 0.5 per cent solution.[30]

Several thousand patients, including many who were poor risks, chroni-

cally ill Asiatics and Africans, have been treated with one or more of the diamidines. Deaths due to delayed poisoning have been reported by Bowesman [9] and Kirk and Henry.[10] The fatalities were due to combined hepatic and renal injury. It should be noted that solutions were used which had been prepared in England and shipped to Africa by air. It is now known that such solutions are unstable and become toxic. These reports emphasize the fact that stilbamidine solutions must be prepared just before administration.[20]

Observations have now been made on four patients with systemic blastomycosis. Three patients have received what we believe is minimal adequate therapy with stilbamidine, while the fourth, due to uncontrollable circumstances, has received insufficient therapy.

Case Reports

Case 1. A 26 year old Indian was admitted to a hospital on July 15, 1950. Dysphagia, present for about one year, had been so severe during the previous five months that the patient had lost about 40 pounds in weight. An esophagram made on July 23 showed a stricture of the esophagus. Esophagoscopy on July 28 showed a grossly malignant appearing lesion at the junction of the upper and middle thirds of the esophagus, but biopsy did not show malignant cells. Mirror laryngoscopy on August 3 was negative. Esophagoscopy was repeated on August 5 and biopsy again did not demonstrate neoplastic changes. Attempts to pass a bougie resulted in a perforation into the mediastinum. The mediastinitis responded to conservative treatment. A gastrostomy was performed on August 15 because of continued difficulty in swallowing. Fluoroscopy and roentgenograms, made after swallowing Lipiodol on August 25, showed a fistula from the esophagus into the mediastinum. Lipiodol was also seen in the trachea, the right main bronchus and its larger subdivisions, indicating the presence of an esophagotracheal fistula. A mediastinal abscess was also demonstrated at these examinations.

On August 28 an effusion in the posterior mediastinum, as well as an anterior mediastinal abscess, containing 200 c.c. of purulent material, was drained. Aerobic and anaerobic cultures made from material in the posterior mediastinal collection were sterile. The same results were reported from material in the anterior mediastinal abscess, except that one culture showed a "yeast" which was reported as a probable contaminant. The patient did well postoperatively. Mirror laryngoscopy on October 4 showed that the right side of the epiglottis, the right side of the larynx and both vocal cords were red and edematous. Although the presence of a carcinoma had never been proved, the patient was transferred to another hospital with the diagnosis of annular carcinoma of the esophagus, esophagotracheal fistula and bronchopleurocutaneous fistula. At the second hospital the diagnosis of carcinoma of the esophagus was not confirmed, and it was recommended that the patient be sent to a center for thoracic surgery in the Veterans Administration.

The patient was admitted to the Veterans Administration Hospital, Fort Howard, Maryland, on November 8. His condition was unchanged from that described above. The roentgenogram of the chest showed a bilateral pulmonary infiltration (figure 1). The epiglottis was thick and covered with a granular friable lesion. A mucosal erosion was seen in the left main bronchus about 2.5 cm. below the carina. The upper portion of the esophagus was red and roughened, and an obstruction was encountered about 2.5 cm. below the cervical constriction. Biopsy from the epiglottis showed that the infection was due to *Blastomyces dermatitidis*. Three hundred thousand

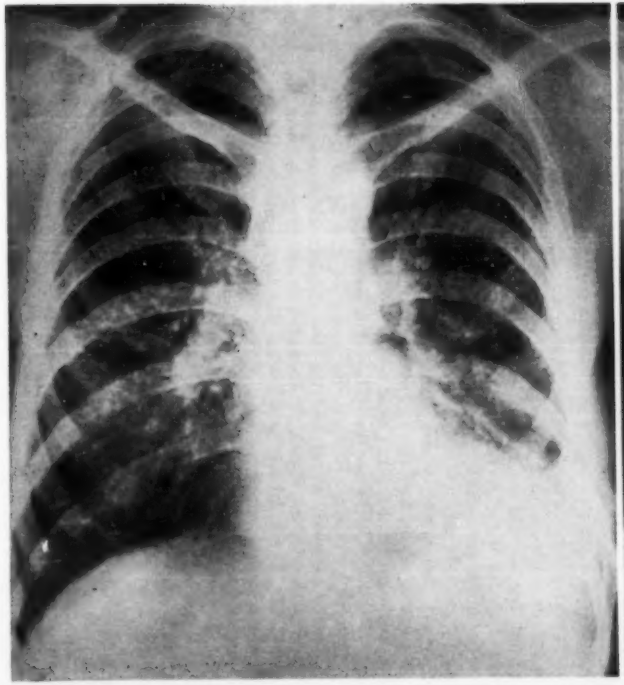


FIG. 1. Roentgenogram of chest of case 1 on November 9, 1950.

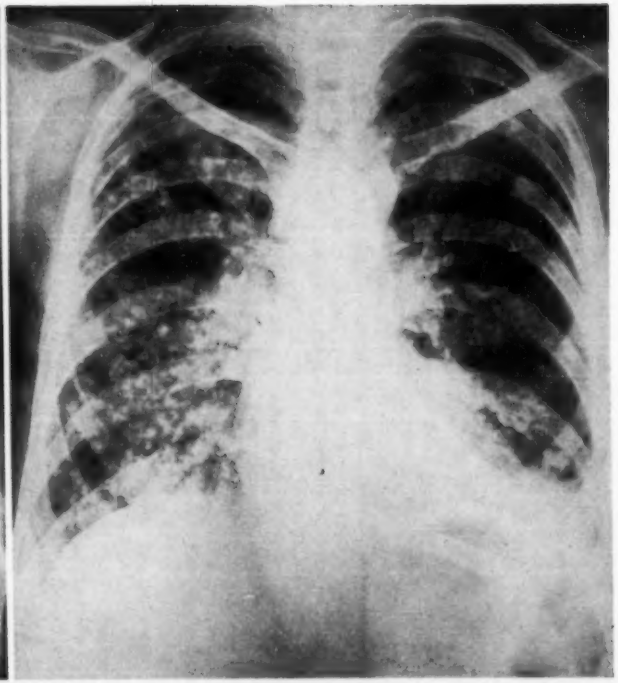


FIG. 2. Roentgenogram of chest on December 12, 1950, before initiation of treatment.

units of aqueous crystalline penicillin G were given intramuscularly daily from November 25 through December 13. An abscess in the lower portion of the anterior cervical region was incised and drained. *Blastomyces dermatitidis* was isolated from cultures of the purulent drainage material. An increase of the bilateral pulmonary infiltration was noted on the roentgenogram (figure 2).

The patient was placed on a low protein, low purine diet on December 15, and treatment with stilbamidine and propamidine * was started on December 16. Since fibrin and desoxyribonucleoprotein are important components of inflammatory exudate, it seemed well to remove them from the involved areas by using streptokinase and streptodornase.† Twenty-five thousand units of streptokinase and 15,000 units of streptodornase dissolved in 5 c.c. of physiologic saline were inserted into the left bronchopleurocutaneous fistula. After an incubation period of four hours the wound was washed with 3 c.c. of physiologic saline, and 5 c.c. of 0.1 per cent solution of propamidine in 5 per cent glucose in distilled water was inserted into the fistula. The nasopharynx was sprayed with a saline solution of the enzymes, and after four hours the solution of propamidine was sprayed into the nasopharynx. Five one-hundredths of a gram of stilbamidine in 100 c.c. of 5 per cent glucose in distilled water was given slowly intravenously.

On December 18 the intravenous dose of stilbamidine was increased to 0.1 gm. All other treatment was continued as outlined. In addition, the topical application of 25,000 units of streptokinase and 15,000 units of streptodornase to the wound in the neck was employed. The amount of stilbamidine was increased to 0.15 gm. on December 20. By December 22 the wound in the neck was unusually clean but was slow in healing. Daily treatment with 0.15 gm. of stilbamidine intravenously was begun on December 22 and continued through January 3, 1951. Marked improvement in the patient's general condition occurred. A gradual decline in the febrile course was noted, and the temperature reached normal limits by January 5.

Laryngoscopy was performed on January 10 and the inflammatory condition present was seen to have receded considerably. The epiglottis was still somewhat thickened. Biopsy showed only a few poorly defined *Blastomyces dermatitidis*. Comparison with previous examinations showed a remarkable change in the amount and degree of inflammation and cellular changes in the epithelium. The roentgenogram of the chest at this time did not show much change (figure 3).

A second course of therapy, similar to that just described, was initiated on January 19. The initial dose was 0.15 gm. and was continued daily through February 1. Laryngoscopy on February 16 showed progressive resolution of the inflammatory process. Biopsy showed only a rare *Blastomyces dermatitidis* in scarred connective tissue. The lesions on the arm and face had dried up.

A third course of stilbamidine was begun on March 5 and continued through March 15. No toxic effects from the stilbamidine were noted. The patient had continued to improve generally. His appetite was good and he gained 37 pounds in weight. The esophagomediastinal and the bronchopleurocutaneous fistulae closed. Laryngoscopy performed on March 27 showed a complete recession of the inflammatory condition. The epiglottis was healed, although scarred. Biopsy from the epiglottis did not show *Blastomyces dermatitidis*.

The patient was admitted to the hospital again on September 18. During the interim he had continued to improve. His weight at this time was 144 pounds. His hoarseness, which had been severe and persistent, had disappeared. Numbness was noted bilaterally over the malar portions of the face. The stricture of the esophagus was still present.

* The stilbamidine diisethionate and the propamidine isethionate were supplied by Merck and Company, Incorporated.

† The streptokinase and the streptodornase were supplied by Lederle Laboratories Division, American Cyanamid Company.

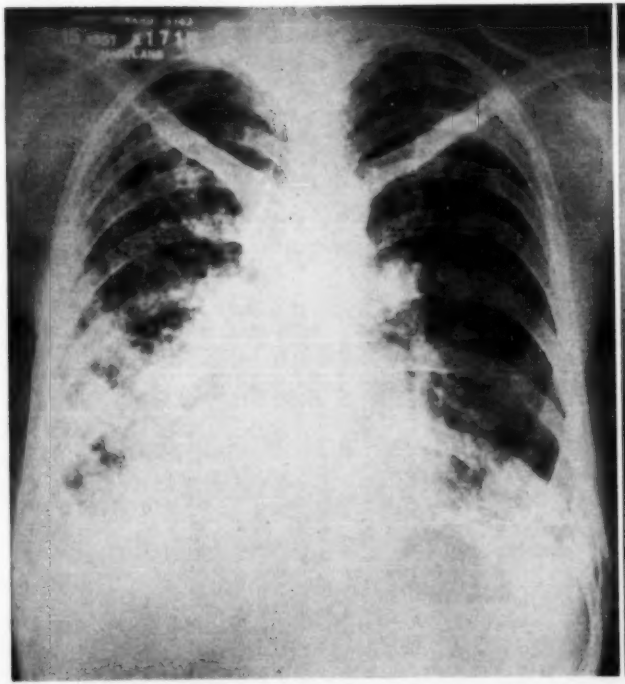


FIG. 3. Roentgenogram of chest on January 15, 1951, after completion of first course of stilbamidine.

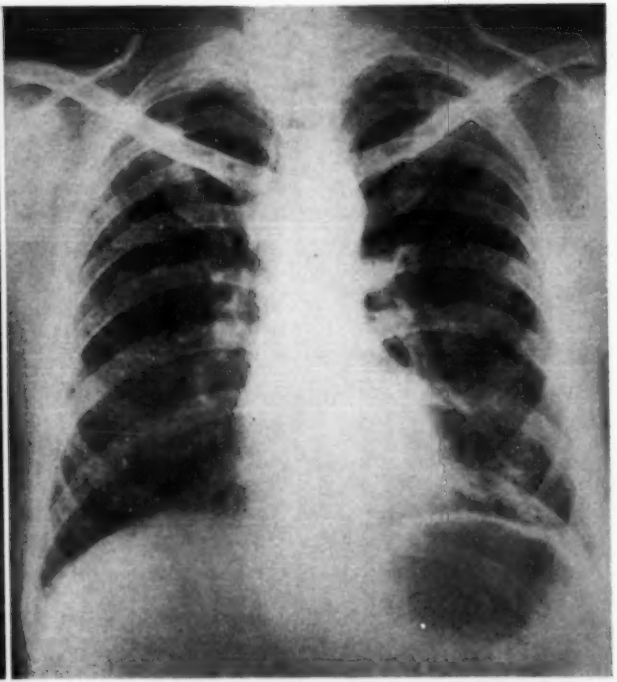


FIG. 4. Roentgenogram of chest on September 9, 1951, on follow-up examination.

Objective neurologic findings were not present. Laryngoscopy and bronchoscopy showed a normal epiglottis, larynx and bronchial tree. At esophagoscopy a bougie could not be inserted past the stricture.

The roentgenogram of the chest showed a remarkable reduction in the amount of infiltration of the lungs (figure 4). By means of Lipiodol given by mouth and a thin suspension of barium given through the gastrostomy, a stricture of the esophagus just above the level of the aorta was demonstrated.

Case 2. A 32 year old white female was admitted to the United States Marine Hospital, Baltimore, Maryland, on March 12, 1951, with a history of cough and pain in the chest of three months' duration. In November, 1950, she had had a low grade fever, stabbing pain between the scapulae and a dry cough. She was treated at another hospital for three weeks, during which time her symptoms responded to penicillin, aureomycin and one of the sulfonamides. On the roentgenogram of the chest a lesion was found in the medial portion of the left upper lung field. A diagnosis of "virus" pneumonia was made. In January, 1951, her symptoms recurred. Further roentgenograms of the chest were made by another physician, who then referred the patient for treatment with a diagnosis of tumor in the left lung. The patient was found to be pregnant. Laboratory examinations were normal. The skin test for blastomycosis in a dilution of 1:10 and the complement fixation test were negative. The roentgenogram of the chest on March 12 (figure 5) showed a marked density extending upward and somewhat outward in the upper section of the root of the left lung. Bronchoscopy on March 13 was negative.

At thoracotomy on March 29 a mass about 7 cm. in diameter was found in the upper part of the lower lobe. The lesion extended to a depth of about 1 cm. into the lung and was attached to the chest wall between the fourth and fifth ribs. The central portion of the tumor was necrotic. A piece of the tumor was removed for biopsy. The diagnosis at the time of operation was carcinoma of the lung with invasion of the chest wall, but the report of biopsy was *Blastomyces dermatitidis.*

The patient had received 0.5 gm. of aureomycin orally four times a day from March 17 to April 9. Three hundred thousand units of aqueous crystalline procaine penicillin G were given intramuscularly twice a day from March 29 to April 4.

Treatment with stilbamidine was started on March 31 with 0.05 gm. intravenously. One-tenth of a gram was given on April 1 and 0.12 gm. on April 2 and April 4. Between April 6 and April 25, 10 doses of 0.15 gm. were given at intervals of approximately two days. A second course of 12 treatments was given of 0.15 gm. at almost daily intervals between May 9 and May 21. A third course of 12 treatments at the same dosage was given between June 1 and June 12.

The patient improved under treatment. Improvement was also indicated by serial roentgenograms of the chest (figures 6 and 7). Evidence of a neuropathy was not found at the completion of treatment. The patient was discharged on June 14. A roentgenogram of the chest, taken elsewhere on July 20, 1951, and forwarded, showed complete regression of the lesion.

A letter dated September 1 stated that the patient was feeling well, that her pregnancy was progressing normally and that her weight was 135 pounds. For about the past month a numbness and loss of feeling had been present in the face, particularly about the forehead and lips, but the patient was otherwise well. In a letter dated November 4 it was stated that the patient had given birth to a living female child. The patient complained of a crawling, itching and tingling over the skin of the face which was more severe around the eyes and lips. The lips felt swollen. The patient felt well as far as her original disease of the chest was concerned.

Case 3. A 42 year old white male was admitted to the Medical Service of The Johns Hopkins Hospital, Baltimore, Maryland, on October 19, 1951, for further

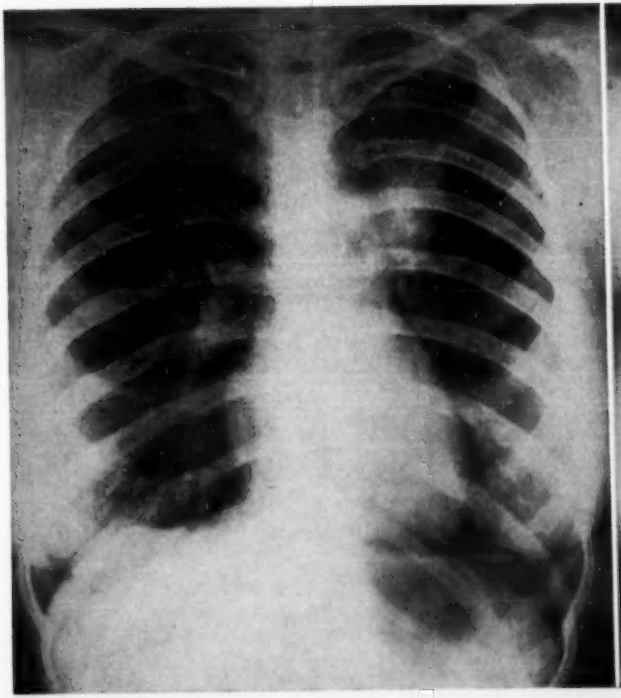


FIG. 5. Roentgenogram of chest of case 2 on March 12, 1951, showing marked density in upper section of the root of the left lung.

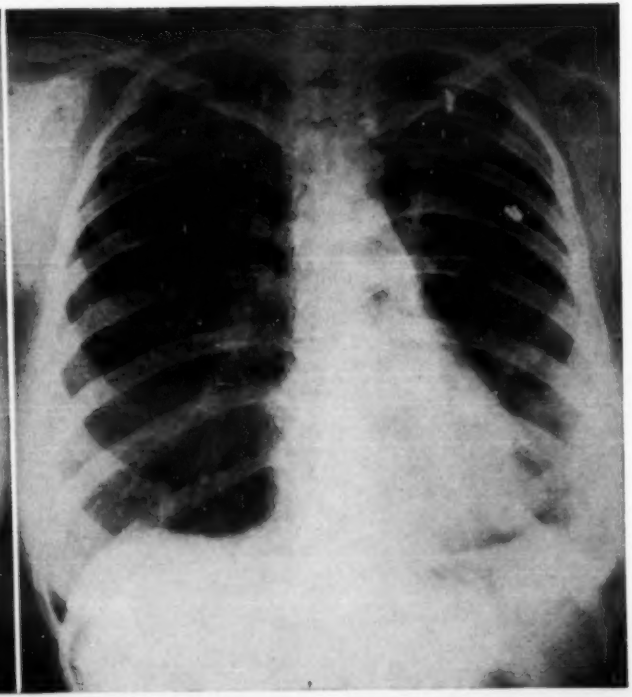


FIG. 6. Roentgenogram of chest on May 10, 1951, showing regression of lesion.

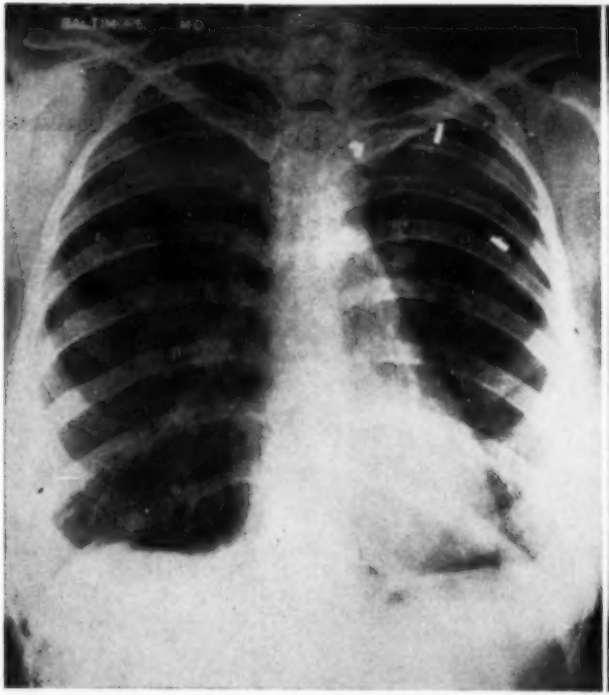


FIG. 7. Roentgenogram of chest on June 8, 1951, showing almost complete regression of lesion.

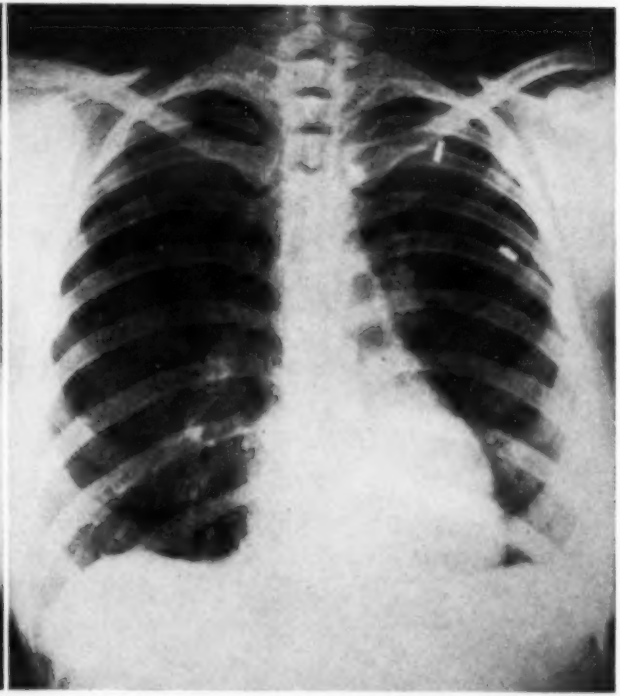


FIG. 8. Roentgenogram of chest on July 20, 1951, showing complete regression of lesion.

therapy for a systemic blastomycosis. For four years the patient had had progressively enlarging lesions of the face until it was almost completely involved. The patient had been to many hospitals and had been treated at different times with roentgen therapy, vaccine and potassium iodide. Three years ago a right orchiectomy and epididymectomy had been performed at The Johns Hopkins Hospital and blastomycosis was found. Streptomycin had been given without benefit. Two years previously a course of actidione was unsuccessful. Vaccine was not beneficial. At the time of his third admission an extension of the lesions into the external auditory canals had occurred. Eating was difficult because he could not open his mouth. A severe degree of keratitis and blindness with perception of light only was present in the left eye. The prostate was enlarged and irregular. The patient was given 0.05 gm. of stilbamidine intravenously on September 10, 0.1 gm. on September 11 and 0.15 gm. daily from September 12 through September 25. A solution of 0.1 per cent propamidine was applied to the external lesions for 20 minutes three times a day

FIGS. 9 and 10. Facial lesions of case 3 before stilbamidine therapy.

during this period. The patient was discharged after this course. A progressive resolution of the cutaneous lesions was noted and, upon rehospitalization one month later, a second course of stilbamidine consisting of 0.15 gm. was given daily from October 21 through November 5. Further resolution of the cutaneous and prostatic involvement was observed. Symptoms related to a trigeminal neuropathy were not seen.

Case 4. A 34 year old white male seen at the University Hospital, Baltimore, Maryland, had systemic and cutaneous blastomycosis. Treatment had been varied and intensive. Penicillin, aureomycin and chloromycetin had been given without benefit. Iodides had been administered orally and intravenously. The patient was subsequently desensitized and iodide therapy given again. Stilbamidine was advised for this patient but, due to uncontrollable circumstances, he never received the necessary amount of the drug. Some improvement was manifest. Excision of the resolv-

FIGS. 11 and 12. Three weeks later after a single course of stilbamidine therapy.

FIGS. 13 and 14. After completion of therapy, November 30, 1951, and plastic repair of the region about the eyes.

ing lesions was performed. The patient received only 2.2 gm. of stilbamidine over a period of time. Biopsy of a portion of the remaining lesion on the right foot at the time of excision and closure after treatment had been interrupted revealed *Blastomyces dermatitidis*. The patient developed numbness and paresthesia of the forehead, nose

and cheek due to a trigeminal neuropathy about four months after treatment had been discontinued. Although treatment was unfortunately inadequate in this patient, three observations are valuable. (1) Continued therapy until 4.5 to 6 gm. had been given would probably have resulted in cure, since a good response was seen even with the 2 gm. given. (2) Two grams of stilbamidine are not sufficient to eradicate *Blastomyces dermatitidis*. (3) This amount of drug is sufficient to produce a trigeminal neuropathy after a latent period.

Comment

Stilbamidine and propamidine have produced favorable therapeutic effects in patients with blastomycosis. The amount of stilbamidine for cure is not known, but probably 4.5 to 6 gm. administered in two or three courses are sufficient. The patient in case 1 received a total of 6 gm.; case 2, 5.5 gm.; case 3, 4.5 gm., and case 4, inadequately treated but still showing a response, 2.2. gm. Noteworthy is the fact that *Blastomyces dermatitidis* could still be isolated from a lesion in the latter patient after a total of 2.2 gm. A trigeminal neuropathy became evident in cases 1, 2 and 4 but has not yet appeared in case 3. This complication has been annoying but not disabling. Other evidence of toxicity has not been observed. Propamidine can be used locally to advantage but should not be given parenterally because of its toxicity.

Summary

Beneficial results have been obtained in three patients with blastomycosis and an encouraging result in a fourth in whom therapy could not be completed. Further trial of stilbamidine and propamidine for the therapy of blastomycosis is suggested.

Addendum

Since this manuscript was submitted, the authors have been informed of seven additional cases of blastomycosis treated with stilbamidine, in which similar beneficial response was observed. Two patients treated with 2-hydroxystilbamidine by Snapper et al. (Snapper, I., Schneid, B., McVay, L., and Lieben, F.: The pharmacology and therapeutic value of diamidine derivatives, Trans. N. Y. Acad. Sc., in press) have also shown regression of their lesions.

Acknowledgment

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ON THE ORIGIN AND ESSENCE OF THE MORGAGNI-ADAMS-STOKES SYNDROME *

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I. INTRODUCTION

MORGAGNI [1] observed this syndrome and described it accurately in 1765. Adams [2] observed it in 1827 in a 68 year old patient. Stokes [3] mentioned five cases in 1846. Adams and Stokes found their patients to have fatty degeneration of the cardiac muscle, and considered this to be the cause of the slow pulse and attacks of syncope.

When the brothers Weber and Budge discovered in 1846 that the vagus nerve exerted a retarding influence on the heart, the concept that this action caused the Morgagni-Adams-Stokes syndrome came more and more to the fore. This theory has been able to hold its own up to the present, at least in some cases. Before dealing with the more modern concepts of this syndrome, it is necessary to sketch the clinical picture.

Bystanders may not notice attacks of very short duration; the physician will observe them and see the staring eye and the alternate etiolation and blushing. The patient may "see stars," become dizzy and suffer abnormal sensations. These symptoms, of short duration, may introduce a severe attack. The patient may just have time to get out of the busy street before he falls and turns as pale as death. Convulsions involving the whole body may follow. Respiration becomes rattling and urine and feces are voided. All these symptoms do not invariably occur, and an attack may be interrupted at any moment. The face then flushes again, and, after a brief attack, recovery is rapid. The frequency and seriousness of attacks vary considerably with different patients. Sometimes only one or a few occur, sometimes there is a long series of attacks.

II. ATTACKS CAUSED BY THE PRE-AUTOMATIC PAUSE

Many theories concerning the mechanism of the Morgagni-Adams-Stokes syndrome were formulated during the last century, but modern concepts date back only to 1892 and 1893, when the atrio-ventricular bundle was discovered by Kent [4] and His.[5] In 1885 Chauveau [6] had already observed heart block with certainty in a patient who showed the syndrome of Morgagni-Adams-Stokes. In 1899 His [7] mentioned an example of this syndrome which he ascribed to heart block. In 1906 our compatriot Goteling Vinnis [8] described a case in which heart block was present. In 1909 Volhard [9] mentioned eight cases. He observed that the attacks arose when, during the

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transition from partial to total block, the ventricles paused for a moment before their own rhythm appeared. Volhard was of the opinion that the attacks were always caused by this ventricular pause—the "pre-automatic pause."

Gallavardin [10] and Wenckebach [11] endorsed this view. They supposed that a progressive pathologic process was the cause of the heart block. This explanation was adequate as long as only one attack occurred; usually, however, there were a large number of attacks. To account for this they supposed that the heart block returned again and again. Thus a temporary depression of conduction was supposed to result from disturbances of the circulation, from exacerbation of an inflammatory process, from a neurotic reflex influence, or from vagal or accelerator nerve actions. Erlanger [12] also found as a result of his experiments, in which he pinched off the bundle of His, that an acceleration of auricular contractions might abolish conductibility between the auricles and ventricles. Griffith and Cohn,[13] Volhard and Wenckebach and others observed clinically that the attacks of Morgagni-Adams-Stokes were often introduced by an acceleration of the auricles.

Thus the earlier clinicians attempted to explain the fact that these attacks could recur frequently, at the same time maintaining that they were caused, in patients with block, by the pre-automatic pause. On the other hand, various clinicians, including Volhard, Wenckebach and Gallavardin, considered that when heart block persisted it must rather afford relief to the patients, as a safe harbor from attacks. Gallavardin even speaks of "la conquête de son automatie ventriculaire."

The pre-automatic pause may certainly cause some attacks of Morgagni-Adams-Stokes. Just how often this happens may be shown by a continuous registration of these attacks with the string galvanometer. In any event, it can now be considered certain that only a small fraction of attacks can be ascribed to a pre-automatic pause. This may become obvious from the following explanations.

III. Attacks Arising During Complete Heart Block

(A) *Ventricular Fibrillation or Flutter.* We have seen that 30 years ago Wenckebach and Gallavardin considered the pre-automatic pause to be the only cause of Morgagni-Adams-Stokes attacks. When complete heart block became permanent the patient, according to their view, had arrived in a safe harbor. This concept was disproved by my publication in 1923.[14] I registered an electrocardiogram in 1921 on a 60 year old female patient during Morgagni-Adams-Stokes attacks; she suffered from Bright's disease and was sent to me by the director of the "Binnengasthuis" of Amsterdam. She had attacks of syncope lasting one or two minutes, during which the pulse disappeared. Brief lapses of the pulse also occurred during which consciousness was not lost. The heart was somewhat enlarged to percussion

and a systolic souffle was heard, most distinct at the base of the heart. I connected her to the string galvanometer for two hours and recorded the electrocardiogram; during this time she had one attack after another. Thus I obtained records of a large number of brief attacks, from which it was evident that during each attack ventricular flutter, or a transition from ventricular flutter to fibrillation, was present. The tracings also showed that there was no relationship between the P waves and the ventricular complexes, so that complete heart block was present. A month later I again registered her electrocardiogram; the ventricular complexes were quite regular and showed a slow rhythm that was independent of the much quicker auricular oscillations. In figure 1 some brief attacks are represented.

A second case, in which the attacks during complete heart block were caused by ventricular fibrillation, was published in 1924 by Gallavardin and Bérard.[16] In 1925 von Hoesslin [16] published a third case; ventricular flutter was present during complete heart block. Levine and Matton [17] described a similar case in 1926. In the same year I drew attention to the fact that in all these four cases the form of the ventricular complexes was atypical even when ventricular flutter or fibrillation was not present. These ventricular systoles, therefore, arose from an ectopic focus in one of the two ventricles. The contraction waves originating from such a point can, therefore, easily start circulating in one direction provided the metabolic condition of the ventricular muscle has deteriorated. The ventricles are then in a situation similar to the normal auricles in which the normal stimulations originate from a more or less circumscribed point.

In former publications I have pointed out that whereas auricular fibrillation presents itself relatively often, ventricular fibrillation arises much more rarely; this is because, under normal circumstances, the rhythmic stimulations travel to the ventricles along the bundle of His with its arborescent ramifications entering the ventricular muscle at hundreds of points at approximately the same time. All these contraction waves then collide in the ventricular muscle and are extinguished. In this way a coördinated ventricular systole is initiated. The bundle of His, with its arborescent ramifications, stands guard as a protection to the ventricles. Thus ventricular fibrillation can arise only with difficulty; indeed it will only occur if the metabolic state of the bundle of His has deteriorated, so that atrioventricular conduction is limited. In these circumstances the contraction wave starts from a circumscribed, ectopic point and can circulate, so producing flutter or fibrillation. In the light of the circulation theory we can easily understand why auricular fibrillation occurs so often and ventricular fibrillation more rarely; and why, with heart block, ventricular fibrillation arises so readily.

A large number of publications have appeared since the four mentioned above, reporting Morgagni-Adams-Stokes attacks in patients with complete heart block.

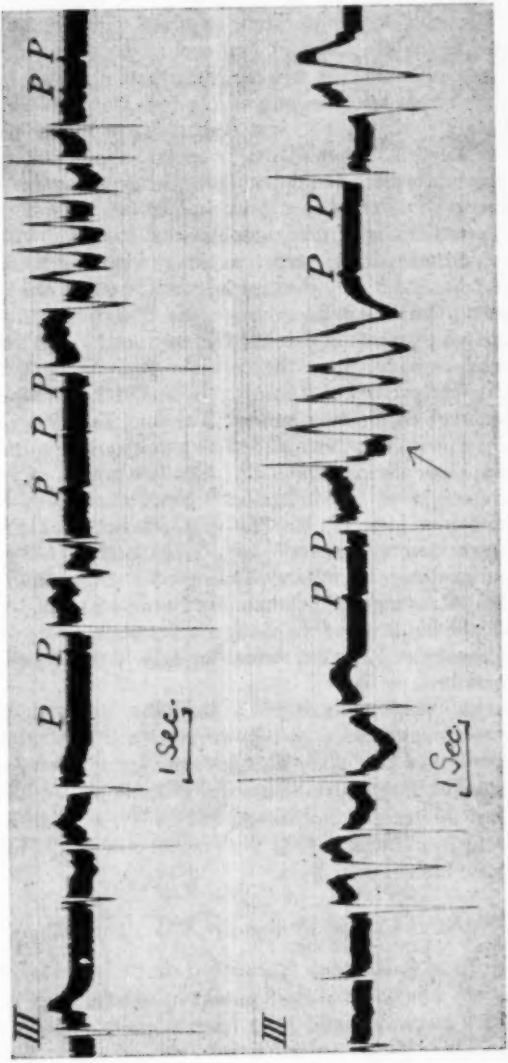

FIG. 1.

(B) *Groups of Luciani During Complete Heart Block.* In 1873 Luciani [19] described a rhythm in frog hearts which we now know as "periods of Luciani." Pauses of longer duration alternate with groups of systoles. This type of cardiac rhythm may be thought of as analogous to the periodic breathing of Cheyne-Stokes. In a somewhat unusual way it became clear to me that this rhythm may be responsible for Morgagni-Adams-Stokes attacks. In 1928 Dr. Kleyn, who was then assistant in the clinic of Professor Kühne at Leyden,[20] showed me an electrocardiogram of a patient afflicted with these attacks. I did not immediately recognize the periods of Luciani. Later Dr. Kaaskooper [21] worked in my laboratory and took a great many electrocardiograms of patients with Morgagni-Adams-Stokes attacks. Some of these attacks were caused by ventricular fibrillation or flutter; in three other cases they resulted from standstill of the ventricles or of the whole heart. Later it became clear to me that in these three patients we were dealing with periods of Luciani.[24] Because in such electrocardiograms the pauses are so far apart they are not easily recognized, but they are without doubt the periods of Luciani. In one of Kaaskooper's patients eight pauses occurred within two hours. The long duration of the intervening groups can in no way be regarded as an objection to the diagnosis. Indeed, in his experiments Langendorff [22] described groups of Luciani having a duration of one hour. Complete heart block was present in Kuenen's patient and in the three patients observed by Kaaskooper. This fact is also in accord with experimental findings. In 1917 I found I could easily obtain periods of Luciani in frogs' hearts by pinching off the auricles.[23] If, therefore, the ventricle shows a great inclination to form periods of Luciani when withdrawn from the influence of the sinoauricular node in the experimental heart, so in clinical heart block the ventricles may likewise show a similar inclination to form such periods.

A patient with complete heart block therefore has a double risk of Morgagni-Adams-Stokes attacks: both from ventricular fibrillation or flutter, and also from periods of Luciani. Thus it is not justifiable to ascribe sudden cardiac deaths exclusively to ventricular fibrillation, as has been customary in the last 30 years. Cardiac standstill may, as well, be the cause of sudden death, as I indicated in 1932.[24] The old concept of heart paralysis has, in a way, come into its own again.

IV. Attacks Caused by Paroxysmal Bradycardia

Lutembacher [25] and Gallemaerts [26] described another mechanism. Lutembacher had a patient who suffered from flatulence and a general enteroptosis. This patient had a pulse rate of 60 per minute which might suddenly fall to between 30 and 24. This retardation occurred as a result of 2:1, 3:1 or 4:1 auriculoventricular block. Syncope coincided with the sudden fall in pulse rate.

Gallemaerts' patient also suffered from a general enteroptosis. As with Lutembacher's patient, the pulse might drop from 70 or 80 per minute to 30, and then the attack of syncope would occur. The slow pulse in this case resulted from the sudden development of complete heart block, not preceded, however, by a pre-automatic pause.

V. Attacks Caused by Sudden Appearance of Bigeminy *

From 1932 on it was evident to me that Morgagni-Adams-Stokes attacks might also arise when the pulse rate dropped considerably without the appearance of true bradycardia. A possible mechanism is bigeminy, in which the extrasystole follows the preceding normal systole so rapidly that little or no blood is emptied into the aorta; in such circumstances the pulse rate is halved. But my conclusion anticipates the facts. For it was not so easy and obvious as it sounds when I had to diagnose my first case.

The facts are as follows: In 1932 an aged colleague from The Hague came to me as a patient.[27] His troubles dated from 1924. After lengthy treatment a colleague had advised him to give up his practice; on his advice the patient set out on a journey for 18 months, but his symptoms changed for the worse. After that he moved to The Hague and consulted several cardiologists, without benefit. In 1932 he consulted me, traveling to Groningen for examination. He told me that he had occasional attacks lasting some hours, sometimes even longer. They made him very restless, but his condition was somewhat more tolerable if he remained sitting or lying. He would feel oppressed and anxious, and was incapable of any activity. The attacks began and ended abruptly. The electrocardiograms gave important information. In them I found many extrasystoles and some bigeminal groups. The heart was a little dilated to the left. Auscultation revealed no abnormalities, with the exception of the extrasystoles. I asked the patient the pulse rate during an attack, and also that before and after the attack. He answered that the rate was about 35 to 40 during the attack, and 70 to 80 before and after it. I deduced that my colleague's attacks were due to the sudden development of bigeminy, in which the premature beats followed the normal ones so quickly that little if any blood was ejected into the aorta. I told him my diagnosis and explained the cause of his symptoms, assuring him that he might well live to be 80. At that time he was 69. He was put on a regimen including a prescription containing quinine and strychnine. I do not believe he took the medicine, but my main purpose was achieved. The patient felt reassured and was convinced that my diagnosis was right. The attacks ceased and he traveled again to foreign countries and in mountainous regions, and biked again through The Hague. He lived for many happy years and died at the age of more than 80. This happy experience had taught me a new mechanism for Morgagni-Adams-

* This type was described by me in 1937 (Cardiologia 1: 253, 1937).

Stokes attacks. This type is distinguished from the usual forms by its long duration; the beginning and end of the attack are abrupt, as in the more usual types, and the origin is again cardiac.

The short duration of the more usual attacks is simply due to the fact that longer periods of pulselessness must soon produce death. Thus their short duration is, if I may use the term, an artefact. Pulselessness and brevity are therefore not characteristics of the attacks per se; their only true characteristics are their sudden beginning and termination and their cardiac origin.

There are some clinicians, such as Gonin,[28] who hold that an attack is of the Morgagni-Adams-Stokes variety only if ventricular standstill or fibrillation be present together with acute or permanent disturbances of conduction. It seems to me that such a concept is too narrow. We must not curtail the free development of science by a priori statements. It should be remembered that when Adams and Stokes described the syndrome that bears their names, they were of the opinion that it was caused by a fatty degeneration of the heart muscle.

It seems to me a better and broader concept to consider every disturbance of the action of the heart that begins and ends abruptly, and causes such interruption of the circulation that more or less complete cerebral ischemia results, as part of the Morgagni-Adams-Stokes syndrome.

In a second case of the bigeminal type, conditions were more favorable to diagnosis. The first attack of this patient's syncope occurred in 1932. He came to me in May of 1935.[27] I found his heart enlarged to the left, with frequent ventricular extrasystoles, occasionally bigeminy, and a pulse rate of 60. There were no other abnormalities. In April, 1937, the extrasystoles and groups of bigeminy were still present, and the pulse rate was still 60. I registered an electrocardiogram during an attack of syncope. Lead II of this tracing is shown in figure 2. After four systoles at the slow rate of 60 per minute, we see bigeminy appear in the upper strip in which each extrasystole follows closely after the preceding normal systole. This is the beginning of an attack which lasted 30 seconds, the end of which is seen in the lower strip. In this strip one group of trigeminy and two of bigeminy are to be seen. At the moment that each extrasystole starts there is little or no blood in the ventricles; consequently the pulse rate is halved, dropping suddenly to less than 30. At the end of the attack the pulse at first accelerates, but after a few beats the former rate is resumed. In this patient I could hear with the stethoscope only the first sound of the premature beats. From this case again we learn that Morgagni-Adams-Stokes attacks can occur without disturbances of conduction.

A third case is also of importance.[29] This concerned a 12 year old boy whose heart was dilated to the left and whose urine contained only a trace of albumin. There were no other abnormalities. He suffered from attacks of syncope, of which the first had occurred five or six years before. In Sep-

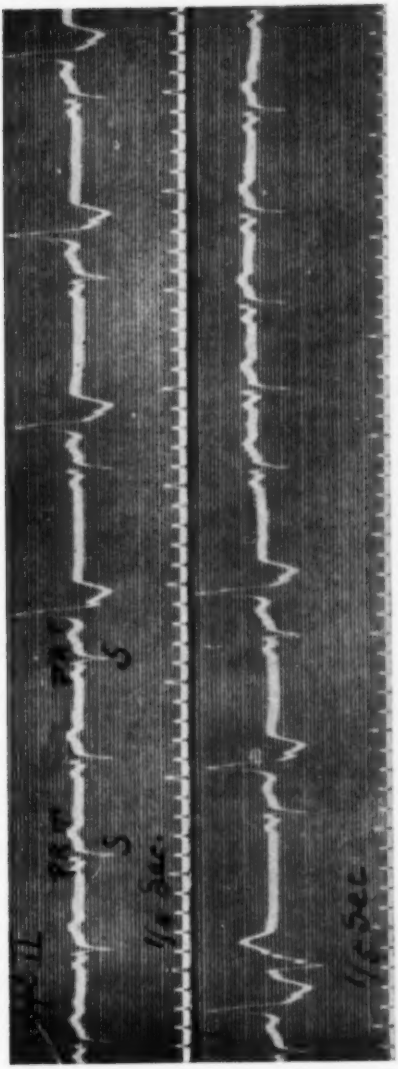

Fig. 2.

tember, 1939, the attending pediatrician had taken an electrocardiogram (figure 3). In all three standard leads, groups of bigeminy are present in which the extrasystoles closely follow the preceding normal systoles. The patient was fully conscious while the tracing was taken. In October, 1940, he was sent to me. On seeing the electrocardiogram of the previous year, I suspected a Morgagni-Adams-Stokes syndrome caused by bigeminy. I recorded a tracing (figure 4) and in Lead I found groups of bigeminy and also groups of three and five systoles. In Lead II only groups of five systoles occur, while in Lead III we see a group of three and further groups of five systoles. We can best analyze the constituents of the groups of five in Lead I; here we can see that the second of the group of five is an interpolated ventricular extrasystole, the third is a normal ventricular complex followed by two further ventricular extrasystoles. It is remarkable that the groups are each time composed of the same sequence. I prescribed quinidine sulfate. On January 15 and June 18, 1941, extrasystoles were no longer present and the patient had had no further attacks.

It seems to me that in this case we must ascribe the attacks to bigeminy or, rather, to recurring extrasystoles. These recurring extrasystoles were superimposed on a normal sinus rhythm and not on a heart block, as in my patient of 1921. Again we must reckon with the fact that Morgagni-Adams-Stokes attacks may be caused by recurring extrasystoles without disturbances of conduction.

VI. The Neurogenic Form

When in 1846 the brothers Weber and Budge found that the vagi exercised an inhibiting action on the heart, it was postulated that Morgagni-Adams-Stokes attacks were caused by vagal inhibition. This theory has continued to command some respect up to the present, although, since the discovery of the bundle of His, it has faded into the background. There remain, however, some cases in which attacks are caused by vagal influence.

First there are those attacks caused by pressure of tumors on one of the vagi, as in the case mentioned by Gluch [30] in 1932. Brandenburger [31] also described three such cases. During the attacks the patients became giddy and lost consciousness. Registration of the electrocardiogram during the attacks showed that disturbances of conduction were not present during or between the attacks. In those three cases, tumors of the parotid were present in adipose and pyknic patients so that, with certain movements of the head, pressure on the carotid sinus resulted. This produced retardation of the heart beat, with resulting syncopal attacks. In all three patients an attack could be provoked with experimental certainty by pressing the tumor against the carotid sinus. Mention may also here be made of the older cases of Starling,[32] Mackenzie [33] and Laslett,[34] in which Morgagni-Adams-Stokes attacks certainly arose from vagal inhibition.

The patient of Flaum and Klima [35] is also worth mentioning. This

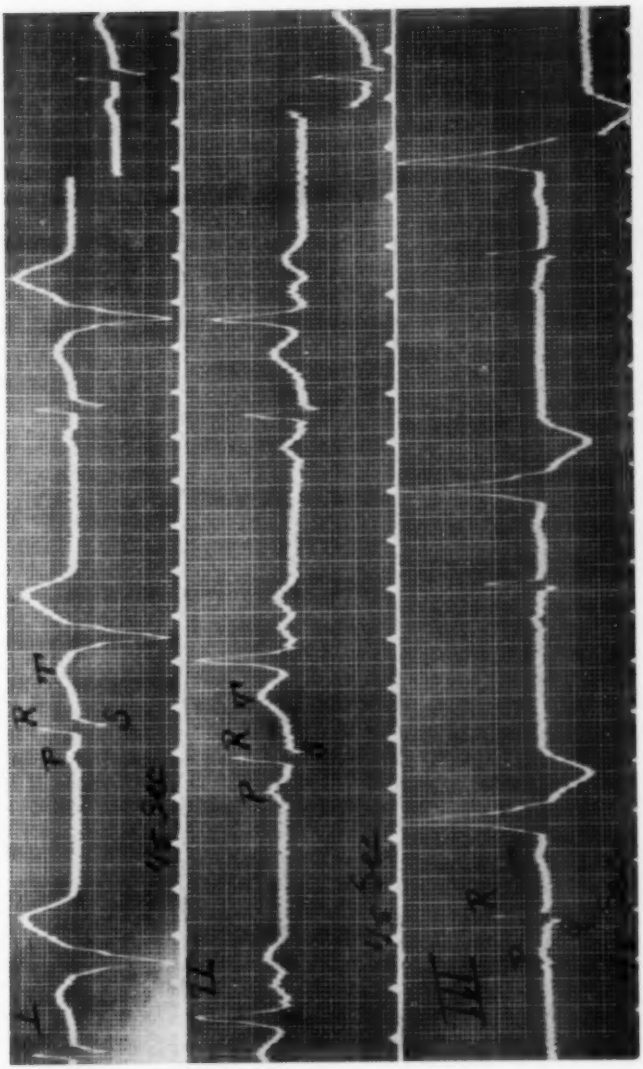

FIG. 3.

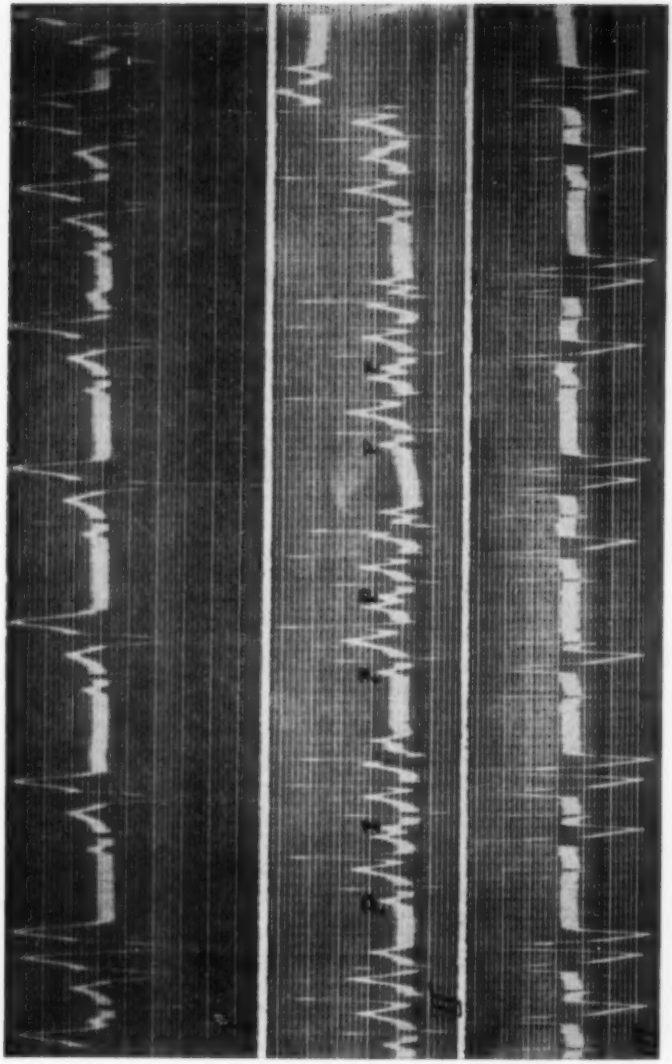

Fig. 4.

patient developed a painful inflammatory affection of the superior laryngeal branch of the left vagus, which caused attacks of syncope from cardiac standstill, together with cramps affecting the trunk and limbs. From the electrocardiogram taken during the attack it was clear that before actual standstill occurred, a gradual slowing of the heart took place. After the superior laryngeal nerve had recovered no further attacks occurred.

The number of cases caused by vagal inhibition does not appear to be large, but we must take it into account in considering the etiology of Morgagni-Adams-Stokes attacks. In my opinion the following case also comes under this heading. In 1940 this patient was employed as a chauffeur by "De Amsterdamsche RytuigMaatschappy." On May 15 of that year he had to transport diplomats to the Hook of Holland, where they embarked on torpedo-destroyers. The motorcar was followed part of the way by German airplanes, and at the embarkment was bombarded. The patient was not hit, but he was badly affected so that he was highly overstrained and nervous. At first the patient, who had never before shown any abnormalities, was troubled with dizziness, "saw stars," and felt indisposed for brief spells. On June 16 he had an attack of syncope. In the autumn the attacks increased to 40 to 50 a day. Between attacks the pulse rate was about 72 per minute, and the blood pressure was 150/100 mm. of Hg. The P-R interval was not prolonged but the electrocardiogram showed left ventricular preponderance. Complete heart block was always present during the attacks, the ventricular rate being 33 per minute and the auricular rate 84. The auricular rate was therefore accelerated over the sinus rate between attacks. The ventricular complexes were not atypical. No abnormalities were to be found along the courses of the vagi.

Dr. Spoor, who treated the patient in the hospital, was of the opinion that the attacks were caused by the nervous condition of the patient, a result of the bombardment; indeed, the physician in charge stated in November, some six months after the bombardment, that the patient gave the impression of being still extremely nervous. I saw the patient for the first time early in 1941, at the request of Dr. Spoor. The diagnosis of Morgagni-Adams-Stokes attacks was not to be doubted. Because of insurance, the question whether a relationship existed between the bombardment and the origin of the syndrome was of great importance. I took my stand against the physician in charge, who denied this relationship because the first attack did not occur until a month after the experience. I pointed out that this reasoning was false, for during that month the patient had had many little attacks of dizziness, "seeing stars," and so on. I then referred to the above-mentioned literature, from which it was clear that attacks of Morgagni-Adams-Stokes might result from vagal influence, and that they could be prevented by atropine. In several of these cases complete heart block resulted from stimulation of the vagi, although the P-R interval was not prolonged during the periods between attacks. It is remarkable that apparently

only those fibers of the vagi that innervate the atrioventricular bundle were stimulated, for heart block resulted while the auricular rate was not retarded.

In 1945 my colleague, Dr. Spoor, found a loud systolic murmur, loudest at the base, and the heart was somewhat enlarged to the left. After a lengthy stay in quiet country surroundings the attacks greatly improved; the number decreased markedly and a normal rhythm prevailed. There were also some changes in the electrocardiogram, namely, in Leads I and II a broadened and obtuse S wave, and in Lead III a broad R′. This may be looked upon as a Wilson-block.

I examined the patient again in 1947, the first time in five years, and found the heart dilated and the vascular trunk a little broadened; but the patient was a tall and robust man and these changes were not great. Figure 5 shows the electrocardiogram. In Lead I a Q wave is present, a broad-

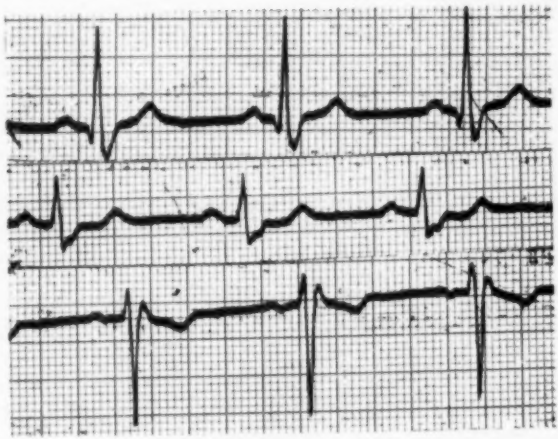

Fig. 5.

ened R wave, and an obtuse S wave. R_2 is lower than R_1 and is also broadened; a broad but not deep S wave is present in Lead II, and a positive T wave. In Lead III the R wave is small and narrow (duration 0.03 second); there is a deep S wave and a broad R′ wave.

In December, 1947, my colleague, Dr. de Langen, made another important finding. Although the patient had had no attacks for a long time, Dr. de Langen was able to provoke mild attacks of short duration by an emotional conversation, by producing sudden loud noises, or by reminding the patient of the bombardment. During the attacks the pulse disappeared and a block of brief duration appeared, but without syncope. Dr. Durrer, who had also investigated the patient, thought that calcification of the aortic valves was present and explained the systolic murmur.

The following facts in this case are important:

1. The Morgagni-Adams-Stokes attacks began following the bombardment.
2. Heart block was present during the attacks, while the auricular rate was accelerated.
3. At first the attacks occurred very frequently, but later, in a quieter environment, less frequently.
4. The attacks occurred especially in circumstances that accelerate the heart rate—running, hurrying, climbing stairs, feeling emotion, being frightened, remembering the bombardment.
5. During the attacks heart block always appeared, and afterwards the normal rhythm returned immediately.
6. The P-R interval was never prolonged in the intervals between attacks, even after 10 years.
7. The QRS complexes were not slurred and notched.

Two explanations of the syndrome are possible in this case: (1) a possible anatomic cause is scarring or degeneration of the bundle of His caused by arteriosclerosis; (2) the syndrome may have been caused by the fright and abnormally nervous condition of the patient resulting from the bombardment. In any case one must recognize that a nervous cause does not exclude the presence of arteriosclerosis; and, on the other hand, that a demonstrable mechanical cause does not mean that the nervous condition may be disregarded. If sclerosis of the arteries is the cause, we might expect that this would be aggravated in the course of 10 years and that the consequences of degeneration of the bundle of His would increase. One might reasonably expect the P-R interval to be prolonged, and yet even after 10 years this is not the case. Similarly, the attacks should be worse now than in the beginning, but the reverse is true. Also, the heart block might have been expected to establish itself, but a normal rhythm with a normal P-R interval still prevails. In a quiet environment the attacks appear rarely, but under conditions producing nervous tension—for instance, when the insurance company stops payments—they increase noticeably. If degenerations and cicatrices had appeared in consequence of arteriosclerosis, one might expect the QRS complexes to be slurred and notched, but they have always had smooth contours. All these circumstances plead for a nervous cause and cannot be comfortably coördinated with the progressive course of a sclerosis. Whether the Wilson-block in this case is caused by arteriosclerosis does not affect our argument. Besides, we know that the Wilson-block can be abolished by pressure on the carotid sinus, or by quinidine, or that it may even disappear spontaneously. Cicatrices or degenerations, therefore, need not be considered in this case.

Before proceeding to my final explanation I should like to say a few words about the systolic murmur and the slight dilatation of the heart.

These two signs were found at about the same time, and I am of the opinion that, in consequence of the repeated attacks of block (more than 50 a day), the ventricles filled abundantly and consequently dilated. This dilatation, oft repeated, may have led to a slight permanent dilatation, and a small relative stenosis of the aortic valve may have resulted. We may exclude the possibility that the systolic murmur was caused by actual aortic stenosis produced by arteriosclerosis, because the pulse was well filled these 10 years, and with aortic stenosis the pulse is small. Any attempt to assume an extension of sclerosis of the aortic valves to the area of the bundle of His as the cause of the attacks of Morgagni-Adams-Stokes must be frustrated, in that the cause of the repeatedly appearing and disappearing block is reversible, and that the P-R interval has not prolonged after 10 years; whereas we know aortic sclerosis to have a progressive course.

The reader may object that now, 10 years after the bombardment, the patient would no longer have Morgagni-Adams-Stokes attacks because of that bombardment. To understand this situation we must focus our thoughts not exclusively on the heart but also on the central nervous system. During the bombardment and afterwards many stimuli from the psyche hammered the nuclei of the accelerator nerves and caused as many as 50 attacks of the Morgagni-Adams-Stokes syndrome in a day. Because these attacks are so often repeated, a transformation takes place in the central elements of the accelerator nerves—a "Bahnung" (paving the way), as the Germans call it. Afterwards the stimuli travel much more easily along these elements, and so attacks can arise during fright, or while running, climbing stairs, doing heavy work and so on. The heart and the accelerator nuclei are not concerned with the origin of the stimuli; the stimuli arrive and the heart reacts—by an attack of Morgagni-Adams-Stokes. We can well understand the ready reversibility, provided the arteries of the heart, and more especially those supplying the bundle of His, are not sclerotic and stiffened by calcification. Sclerotic arteries lack the elasticity necessary for such reversibility.

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PNEUMOCOCCAL MENINGITIS IN ADULTS *

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Despite numerous recent optimistic reports concerning the rate of cure in pneumococcal meningitis, a review of 22 adult cases observed at the Morrisania City Hospital from 1943 through June, 1951, resulted in a more pessimistic and guarded prognosis. Although the almost 100 per cent mortality of this disease in the presulfonamide era is well documented, it is of particular interest to note that the cases herein presented were all treated with combined penicillin and sulfonamides. Despite this, 15 patients died, leaving a gross mortality rate of approximately 70 per cent, which is in sharp contrast to a 73 per cent recovery rate recorded by Applebaum, Nelson and Albin.[1] In children, on the other hand, Nemir and Israel [6] recently reported a series of 15 cases treated during the period 1943–1949, of which 14 recovered. It is our belief, nevertheless, that in the present era pneumococcal meningitis in the adult remains a serious disease with a high mortality rate.

Material

Twenty-two consecutive cases of pneumococcal meningitis observed on the medical wards between 1943 and June, 1951, were reviewed. The ages ranged between 14 and 72 years. Every patient, except one, received combined sulfonamide-penicillin therapy. (See table 4 for fatal cases.)

Blood cultures were obtained in 13 cases. Typing of the pneumococci in the cerebrospinal fluid cultures was done in 16 cases. In three fatal cases, autopsies were performed.

Statistics of Deaths and Cures

Table 1 shows the number of deaths and survivals correlated with age groups. In the age group 14–40 years, 57 per cent of all cures and 20 per cent of all deaths occurred, whereas in the 60–72 year group, 47 per cent of all deaths and 15 per cent of all cures were obtained. These figures illustrate the serious prognosis of this disease in the older age group. Waring and Weinstein [7] noted that only about 12.5 per cent patients past 50 years of age were cured. It is noteworthy that only one of our patients died within 24 hours after admission. Omission of this case would result in a corrected mortality rate of 64 per cent. The duration of hospital stay in the remaining 14 fatalities varied from two to 21 days, with half of the cases dying between the second and fifth days.

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TABLE I

Deaths and Cures by Age Groups in 22 Cases of Pneumococcal Meningitis

Age	Deaths	Cures
14–19 years	0	2
20–40 years	3	2
41–49 years	1	1
50–59 years	4	1
60–72 years	7	1

Seven cases (31.8 per cent) of the entire series were cured; four of the seven were in the age group 14–40 years. Young adults seem to have a more favorable outlook. In their review of the literature, Waring and Weinstein [7] found a favorable outcome in nearly one-third of patients between 30 and 50 years of age. The duration of hospital stay was about the same in the cured as in the fatal cases.

ORIGIN OF THE MENINGITIS

As can be seen from table 2, approximately one-third of all the cases developed during pneumonia, and an additional one-third in connection with upper respiratory infections and/or otitis media. Based on a study of the primary site of origin in 409 cases, Waring and Weinstein [7] found that 40 per cent arose from otitis media and mastoid infections and 25 per cent from pneumonia.

TABLE II

Primary Site of Origin in 22 Cases of Pneumococcal Meningitis

	Deaths	Cures	Total
Pneumonia	6	2	8 (36%)
Upper respiratory infection and otitis	5	2	7 (32%)
Primary	1	1	2 (9%)
Head trauma	0	2	2 (9%)
No history	3	0	3 (14%)

The development of meningitis while the patient was under therapy for the primary illness was observed in three cases. In each of these, pneumonia was the original illness. Meningitis developed on the tenth day while the patient was under sulfadiazine in one fatal case, and on the eleventh day during penicillin administration in the other fatal case. In one patient who survived, meningeal signs appeared on the seventeenth day of sulfadiazine administration.

ASSOCIATION OF COMPLICATING DISEASES

Three patients had serious diseases prior to the onset of meningitis. One cured case was being treated with digitalis for arteriosclerotic heart disease and mild failure. One fatal case had carcinoma of the lung, and the other

had carcinoma of the rectum with severe anemia. Also among the fatal cases were one case each of alcoholism and preëxisting hemiplegia. The greater number of associated complications in the fatal cases is worthy of note.

Cultures of Blood and Spinal Fluid

Blood cultures were done in 13 cases. They were positive in eight cases (six deaths and two cures) and sterile in five cases (one death and four cures). The presence or absence of bacteremia per se would therefore not appear to be of great prognostic import. This is also borne out in the literature.[1, 6, 7]

Table III

Spinal Fluid Typing in 16 Cases of Pneumococcal Meningitis

Type	Deaths	Cures
III	3	0
VII	1	0
VIII	2	1
XII	2	1
XIV	2	0
XXII	1	0
XXIII	0	1
XXXI	0	1
XXXV	0	1

Table 3 shows the various types of pneumococci found on culture of the spinal fluid in 16 cases. There were not enough cases of any particular type to warrant statistical conclusions.

Autopsy Findings

Necropsies were obtained in three cases. Case 1117 showed scattered areas of greenish-white pus over the cerebral cortex, a large collection of the same type of pus surrounding the cerebellum, pons and medulla, and lobar pneumonia of the entire right lung with multiple abscess formation. In case 11338, a carcinoma of the right upper lobe bronchus with pulmonary infiltration and necrosis was found. Unfortunately, permission for examination of the brain was refused. Case 402 showed thick green pus covering the cerebellum and extending over the upper spinal cord, bronchopneumonia of the entire right lung and chronic bronchiectasis.

Therapy

Every case received intensive sulfadiazine therapy, usually by oral and intravenous routes. In addition, all but one (case 1268) had intramuscular penicillin. Although the dosage of intramuscular penicillin ranged between 5,000 and 20,000 units every three hours in the first nine deaths, intensive medication was begun in 1949 for the last five fatal cases. Four of the fatal cases in 1950 even received doses of 1,000,000 units every two hours follow-

TABLE IV

Analysis of 15 Fatal Cases of Pneumococcal Meningitis

Case No.	Age Sex	Date	Hospital Stay	History	Blood Culture	Spinal Fluid Culture	Therapy		
							Sulfadiazine	Units of Penicillin Intramuscularly	Units of Penicillin Intrathecally
1117	50 M	2/6/44	18 days	Pneumonia of right lower lobe. Meningitis developed on the 10th day (during sulfadiazine administration).	Not done	Type 3	Oral and intravenous.	5,000 every 3 hours.	10,000 (3 doses).
1268	50 M	2/10/44	4 days	Right lower lobe pneumonia and marked nuchal rigidity.	Type 3	Negative	Oral and intravenous.	—	—
1936	39 F	3/4/44	8 days	One day history of fever, headache, stiff neck and stupor.	Type 12	Type 12	Oral and intravenous.	10,000 every 3 hours.	10,000 every 12 hours.
10146	53 F	11/7/44	4 days	Upper respiratory infection of one week duration. Semicomatose and marked nuchal rigidity on admission.	Sterile	Type 12	Oral and intravenous.	15,000 every 3 hours.	50,000 (1 dose).
1129	70 F	12/22/44	5 days	Upper respiratory infection and earache for 3 days before admission. Stuporous and rigid neck.	Type 7	Type 7	Oral and intravenous.	15,000 every 3 hours.	25–45,000 daily (4 doses).
11338	63 M	12/29/44	13 days	Chronic cough, weight loss, anorexia and right chest pain. X-ray of chest showed dense infiltration at base of right upper lobe, with trachea and mediastinum displaced to the right. Developed meningeal signs on 10th hospital day and became comatose.	Not done	Type 3	Oral and intravenous.	15,000 every 3 hours.	40,000 (1 dose).

TABLE IV—*Continued*

Case No.	Age Sex	Date	Hospital Stay	History	Blood Culture	Spinal Fluid Culture	Therapy		
							Sulfadiazine	Units of Penicillin Intramuscularly	Units of Penicillin Intrathecally
1866	39 M	3/4/45	3 days	Upper respiratory infection of 1 week duration. Left otitis media of several days' duration. Entered stuporous with rigid neck.	Type 22	Type 22	Oral and intravenous.	20,000 every 3 hours.	50,000 (1 dose).
3546	28 M	4/29/45	1 day	Two day history of painful discharging left ear. Headache and coma developed 1 day before admission. A simple left mastoidectomy was done on 4/29/45 and type 14 pneumococcus was found in the pus.	Type 14	Type 14	Intravenous.	15,000 every 3 hours.	50,000 (1 dose).
5673	61 M	7/7/45	10 days	Headache, nausea and disturbance in vision of 3 days' duration. Admitted with stiff neck, stupor and cloudy spinal fluid. Dullness and diminished breath sounds were present at the right base. X-ray of the chest showed some faint mottling at right base. X-ray of mastoids showed a density on the right suggestive of chronic disease and a normal appearance on the left.	Not done	Negative. Gram-positive diplococcus on smear.	Oral.	20,000 every 3 hours.	30,000 daily.
8977	65 M	10/21/45	2 days	Admitted in coma with stiff neck and temperature 106° F. No history available.	Type 3	Type 3	Oral and intravenous.	20,000 every 3 hours.	—
2496	Elderly female	3/2/49	2 days	Upper respiratory infection two days before admission. Physical examination showed cachexia, severe anemia (hemoglobin, 3 gm.), a carcinoma of the rectum and a stiff neck. Spinal tap showed cloudy fluid. Received blood transfusion.	Not done	Gram-positive diplococcus on smear.	Oral.	100,000 every 3 hours.	10,000 (1 dose).

TABLE IV—*Continued*

Case No.	Age Sex	Date	Hospital Stay	History	Blood Culture	Spinal Fluid Culture	Therapy		
							Sulfadiazine	Units of Penicillin Intramuscularly	Units of Penicillin Intrathecally
402	63 M	1/11/50	8 days	An alcoholic who was found unconscious after a prolonged drinking spree. Marked stiff neck present.	Not done	Untyped pneumococcus.	Oral and intravenous, first 5 days.	150,000 every 3 hours. 1,000,000 every 2 hours, begun 3 days before death.	—
449	43 M	1/12/50	9 days	Ill for 14 days with fever, chills, cough. Treated with penicillin at another hospital. While under therapy he developed meningitis 3 days before his admission to Morrisania Hospital. Physical examination showed fever, stiff neck and pneumonia at right base.	Not done	Type 8	Oral and intravenous.	1,000,000 every 2 hours.	100,000 (3 doses).
2651	72 F	3/11/50	21 days	An old hemiplegic admitted in coma with a rigid neck. Responded rapidly to treatment. Apparently recovered on the 12th day in hospital. Died suddenly 9 days later.	Not done	Type 8	Oral and intravenous.	1,000,000 every 2 hours.	—
4172	54 M	4/20/50	2 days	Admitted with a two week history of preceding upper respiratory infection and a stiff neck of 1 day duration. X-ray of chest showed pneumonia of right middle lobe.	Not done	Type 14	Oral and intravenous.	1,000,000 every 2 hours.	100,000 (1 dose).

ing the article of Dowling and co-workers,[2] which appeared in 1949. Despite this three of these succumbed, while one (case 2651) appeared to have recovered after 12 days of treatment but died suddenly nine days later. Intrathecal penicillin was administered to 11 of the 14 fatal penicillin-treated cases in dosages ranging between 10,000 and 100,000 units per dose. Six of these 11 received only one intrathecal injection of penicillin.

Among the cured cases, the dosage of intramuscular penicillin depended on the general availability of the drug. In the case cured in 1943, only 5,000 units were administered every three hours, whereas the last three cases cured received 1,000,000 units every two to three hours. Three cured cases received no intrathecal therapy, and four cases were given one to five daily intrathecal penicillin injections. It would seem that intraspinal penicillin treatment is not a sine qua non for cure. The following case reports demonstrate the successful cures:

Case Reports

Case 1. J. M. This 51 year old white male was admitted on November 5, 1943, with a five day history of cough, chills and fever and right chest pain. On admission to the hospital he was acutely ill, with classic signs of a right lower lobe pneumonia. He was placed on intensive sulfadiazine therapy but failed to respond to treatment. A chest tap on November 15 revealed no signs of fluid. On November 22, 17 days after admission, his temperature was 104° F. and the neck was rigid. Blood culture at this time revealed growth of pneumococcus type 8. A lumbar puncture showed 3,640 polymorphonuclear cells, and pneumococcus type 8 was obtained on culture. Therapy still consisted of sulfonamides only. On November 27 the patient was comatose, with marked increase in the meningeal signs. Penicillin was then begun, with 5,000 units intramuscularly every three hours and 20,000 units intrathecally once a day. Three days later marked improvement in the patient was noted, and he was considered cured on December 2. However, because of the presence of a persistent shadow at the right base on x-ray of the chest, he remained in the hospital under observation. This was ultimately determined to be a thickened pleura. He was discharged cured on January 14, 1944, after a 70 day hospital stay.

Case 2. A. H. This 45 year old white female was admitted June 11, 1945, with a one day history of headache, fever and vomiting. On admission she was semicomatose, with marked nuchal rigidity. Blood culture was sterile. Lumbar puncture revealed 560 polymorphonuclear cells and pneumococcus type 23 on culture. She received intensive sulfadiazine therapy, together with 20,000 units of intramuscular penicillin every three hours. In addition, she received 50,000 units of penicillin intrathecally on June 12 and another similar dose of 25,000 units on June 14. Her improvement was rapid. All therapy was discontinued on the sixteenth day of admission. X-rays of the skull were negative. X-rays of the mastoids revealed cloudiness on the right with no bone destruction. The left mastoid was normal. She was discharged cured on July 5 after a hospital stay of 24 days.

Case 3. J. F. This 15 year old white boy was admitted January 6, 1947, with a story of head trauma two days prior to his illness, and chills, fever and headache of one day's duration. Physical examination revealed temperature 105° F. and stiff neck, but no other abnormal neurologic signs. A spinal tap was sanguinopurulent with increased pressure. On smear, a gram-positive diplococcus resembling pneumococcus was found. Blood culture and spinal fluid cultures were sterile. He received intensive sulfadiazine intravenously and orally, with 200,000 units of intramuscular

penicillin every three hours. The day after admission he was semistuporous, with marked nuchal rigidity and bilateral Babinski's signs. Lumbar puncture showed the same findings as on admission. On the second day of treatment he recovered consciousness and began to improve rapidly. Several x-ray studies of the skull revealed no evidence of fracture. All sulfonamides were discontinued on the thirteenth day; however, the penicillin was continued for an additional nine days. He was discharged cured on February 3, twenty-eight days after admission.

Case 4. A. M. This 71 year old white male was admitted March 11, 1949 with a story of chills, fever and chest pain of one week's duration. In addition, he was a known arteriosclerotic cardiac who was on a maintenance dose of digitalis. On admission, he was acutely ill, emaciated, dehydrated and comatose. There were signs of pneumonia at the right base. The neck was rigid, and a positive Kernig's sign was present. Blood culture was sterile. Lumbar puncture showed 4,000 polymorphonuclear cells and a pneumococcus on culture. (Typing was not done.) He was treated with intensive sulfadiazine, together with 100,000 units of intramuscular penicillin every three hours. For the first four days he received a daily intrathecal injection of 15,000 to 20,000 units of penicillin. Improvement was marked on the second day of treatment. Thereafter, his progress was favorable, and he was discharged cured on April 2 after a hospital stay of 22 days.

Case 5. P. S. This 40 year old white male was admitted April 16, 1950, with a history of severe earache of two days' duration. He had been hospitalized one week previously with an upper respiratory infection. On admission to the hospital his temperature was 105.2° F. and the right eardrum was injected. The neck was rigid and positive Kernig's and Brudzinski's signs were present. Blood culture showed growth of pneumococcus type 12. Similar organisms were obtained on smear and culture of the spinal fluid, which contained 3,860 polymorphonuclear cells. He was immediately placed on intensive sulfadiazine therapy intravenously and orally, together with 1,000,000 units of penicillin intramuscularly every three hours. On the third day of treatment he was alert and appeared to be making a rapid recovery. A generalized erythematous rash developed on the sixth day and all sulfonamides were discontinued. The penicillin, however, was continued for two more days. Repeated spinal fluid culture was negative, and he was discharged cured on April 26 after 10 days' stay.

Case 6. H. T. This 14 year old white boy fell and struck his head while playing in the street. He became drowsy and gradually lapsed into stupor, and was admitted to the hospital December 20, 1950, as a case of craniocerebral trauma. However, because of fever, marked nuchal rigidity and positive left Babinski's sign, the diagnosis of meningitis was made and the patient was transferred to the medical service. A lumbar puncture revealed cloudy fluid containing 45,000 cells, with 90 per cent polymorphonuclears. He was immediately placed on intensive oral and intravenous Gantrisin, with 300,000 units of intramuscular penicillin every three hours. The next day another lumbar puncture was done and pneumococcus type 35 obtained on smear and culture. A single dose of 100,000 units of intrathecal penicillin was administered, while the intramuscular penicillin was increased to 1,000,000 units every two hours. On December 23 he was alert and the neck was supple. Subsequent lumbar punctures showed no organisms on smear or culture, and marked diminution in pleocytosis occurred. Gantrisin was discontinued after nine days. The penicillin was continued in massive dosage for an additional 10 days. The patient was discharged cured on January 10, 1951 without sequelae.

Case 7. Y. G. This 20 year old white female was admitted on April 28, 1951, complaining of headache, drowsiness and stiff neck. She gave a history of an upper respiratory infection and otitis media one week prior to admission, for which she had received penicillin without relief. Several hours before admission to the hospital she complained of headache, stiffness of the neck and drowsiness. Physical examination

revealed an acutely ill, disoriented and lethargic white female with a temperature of 104.2° F. Acute catarrhal otitis media was seen on the left side. The neck was stiff, and Kernig's and Brudzinski's signs were positive. Lumbar puncture was immediately done and revealed an initial pressure of 340 cm. of water. The fluid was cloudy and showed 24,000 white cells per cubic millimeter, of which 90 per cent were polymorphonuclears. A gram-positive diplococcus was seen on examination of the stained smear of the fluid. Culture of the spinal fluid was subsequently reported positive for pneumococcus type 31. Blood culture was negative. She was immediately placed on 1,000,000 units of penicillin intramuscularly every two hours and 2 gm. sulfadiazine intravenously, followed by 1 gm. every four hours by mouth. The next day she appeared to be improving and her temperature had fallen to 102.2° F. The sulfadiazine was then replaced by Gantrisin, 4 gm. intravenously, followed by 1 gm. four times a day. Her course thereafter was one of steady improvement. Two days after admission she was alert and oriented, although her neck was still stiff. Lumbar puncture at this time showed opalescent fluid, with an initial pressure of 140 cm. of water, and contained 2,030 cells, mostly polymorphonuclears. The culture of the fluid was negative, as were two subsequent cultures. On May 1 only slight nuchal rigidity was found, and her temperature was 100° F. X-rays of the mastoids, sinuses and chest were all normal. She was afebrile on May 2. The sulfonamides were administered for 14 days and the penicillin for 20 days. Sixteen days after she became afebrile all medication was discontinued, and she was discharged on May 22, without sequelae. Telephone conversation with her private physician some months later confirmed the absence of neurologic residua.

Comment

Intrathecal penicillin therapy appears to be falling into disfavor,[4, 5, 6] and our records show that it is not an essential part of treatment. While Lepper and Dowling [4] indicated the importance in prognosis of the presence or absence of coma and of delay in instituting treatment, a study of our fatal and cured cases did not confirm their impressions. The high mortality of this disease in the series of sulfonamide-penicillin treated cases herein reported may be ascribed to the poor nutrition of City Hospital patients and the higher incidence of associated complicating diseases. In addition, we believe that the future routine use of massive intramuscular penicillin (1,000,000 units every two hours) may greatly reduce the present high percentage of fatal cases.

Summary

1. Of 22 adult cases of pneumococcal meningitis observed at the Morrisania City Hospital from 1943 through June, 1951, 15 died (one within 24 hours of admission). This leaves a corrected mortality rate of 64 per cent.

2. This high mortality rate occurred despite combined sulfadiazine-penicillin treatment.

3. No relation could be definitely established between presence or absence of coma, delay in instituting treatment, and the intrathecal administration of penicillin and the ultimate prognosis.

4. Attention is called to the grave outlook for pneumococcal meningitis in the adult, and the necessity for intensive sulfadiazine and massive penicillin therapy.

ACKNOWLEDGMENT

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HEADACHES AND FACIAL PAINS IN CERVICAL DISCOPATHY *

By E. NEUWIRTH, M.D., *Malverne, N. Y.*

ROENTGENOLOGICALLY and pathologically, cervical discopathy is characterized by: decrease, loss or reversal of the physiologic lordotic curvature of the cervical spine, thinning and protrusion of an intervertebral disk, herniation of nucleus pulposus, increased vertebral mobility, vertebral displacement, apophyseal subluxation, constriction and deformation of the intervertebral foramina, hypertrophy of the yellow ligaments, and new bone formation involving apophyseal joints and adjacent vertebrae (discoösteophytosis). A cervical nerve root may suffer irritation or pressure as a result of any of the following pathologic changes of the cervical spine: disc protrusion or herniation; hypermobility, displacement and osteoarthritic changes of the vertebrae adjacent to the pathologic disc.

Due to the foregoing, cervical discopathy may produce a clinical syndrome characterized by segmental sensory, motor and reflex changes. These include cervicobrachialgia, diminution of cutaneous sensibility, decreased muscle power, muscular wasting, and diminution of deep muscle reflexes, especially of the biceps and the triceps reflexes.

In cervical discopathy, however, additional symptoms may occur which are not limited to root areas and which do not seem to be due to involvement of the somatic sensory or motor fibers in the cervical nerve roots. Among such symptoms may be precordial distress simulating cardiac or coronary disease (pseudoangina), dysesthesias, vascular pains and sensation of heat or cold in the fingers, hand and forearm, and facial and cranial pains and dysesthesias.

Ectopic pains, such as headaches, facial pains, anterior chest pains and dysesthesias, have been observed by several authors in patients with pathologic changes of the cervical spine.[1-8] When the well known root symptoms are also present, the site of the pathologic process producing these phenomena is not difficult to determine; but the interpretation of the ectopic pains, especially of the headaches and the facial pains, becomes uncertain and difficult when root manifestations, particularly cervicobrachialgia, are indistinct or absent.

It is pointed out [8] that division of the dorsal cervical roots abolishes only the neuralgia-type pains, e.g., the cervicobrachialgia, but not the dysesthesias, the headaches or the facial and chest pains. Hence, in cervical discopathy, involvement of the sensory fibers contained in the dorsal roots is not responsible for all painful sensory phenomena.

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The surgeon must not divide the ventral spinal roots through which pass the motor and the sympathetic fibers. If, however, root compression is of such degree as to destroy the ventral root, indicated by paralysis and muscular atrophy, the subjective sensory troubles not caused by pathology of the sensory fibers in the dorsal roots either do not develop at all or have disappeared. This permits the deduction that the ectopic pains probably result from involvement of the autonomic (sympathetic) fibers in the ventral roots.

Facial pains in cervical discopathy may appear in such diversified forms that they are apt to baffle even a skillful diagnostician if he is not acquainted with the bizarre characteristics of sympathetic pains. In the effort to discover the underlying cause of the craniofacial pains, dentists, otolaryngologists, ophthalmologists and other specialists are consulted; the skull, the sinuses, the orbits, the jaws and the teeth are x-rayed, and many types of treatment are employed, including surgery, but to no avail. Eventually some patients, despairing of relief, become neurotic and resort to narcotic drugs to alleviate their sufferings. Finally, physicians, unable to discover signs of organic pathology, make an ultimate diagnosis of psychosomatic pains. Such a mistake may be serious, with harmful consequences.

In cervical discopathy the facial pain is constant, with acute exacerbations. The pain varies in intensity but is usually progressive. Acute attacks of pain may be provoked by emotional upsets, cold or heat, humidity, sudden noise or other extraneous factors, but, generally, not by stimulating a circumscribed area, as in classic tic douloureux, or by chewing or talking. Straining at stool, laughing, coughing, sighing and sneezing may also exacerbate the pain. The pain and other symptoms may be precipitated or aggravated by certain extreme movements or certain positions of the head and neck.

The facial pain in cervical discopathy is usually dull and deep seated. A few patients complain of lancinating pains, others of throbbing, smarting or burning pains, as in causalgia. Many patients have a sensation of "pins and needles" in the skin of the face or scalp, or experience formication, numbness, or the sensation of chilliness, of fullness or of puffiness. To obtain relief from the symptoms, the patient often applies pressure to the affected area, or hot or cold compresses.

Topography of Craniofacial Pains

The facial pains and headaches in cervical discopathy at first do not seem to follow any systematic pattern of distribution. At the start they may be confined to a small, poorly defined area, but later on they may extend into the adjacent parts.

Pains unilateral at the onset may later on radiate to the other side of the face and the scalp, where they are less pronounced. A constant discomfort or pain of varied intensity may develop in the supraorbital region and spread

to the forehead and toward the top of the head, and also involve the infra-orbital area, the eyelids, the nasal canthus and the root of the nose. Pulsating and burning pains, felt in the temporal region, may radiate especially to the supraorbital region and the forehead, and also to the zygomatic region and to the ear (figure 1). Pain, often accompanied by decreased visual acuity, may also be felt deep within the eyeball and behind it.

Frequently the area behind the ear, the mastoid region and the side of the neck are the sites of pain (figure 1). One or both ears may feel "plugged"; there may also be tinnitus, clicking noises or even vertigo, as in the Barré-Lieou syndrome.[9] Often the pains are erroneously assumed to originate in the structures where they are felt, for instance, in the eyes, the ears, the tongue, the gums and the lips (orolingual paresthesias).

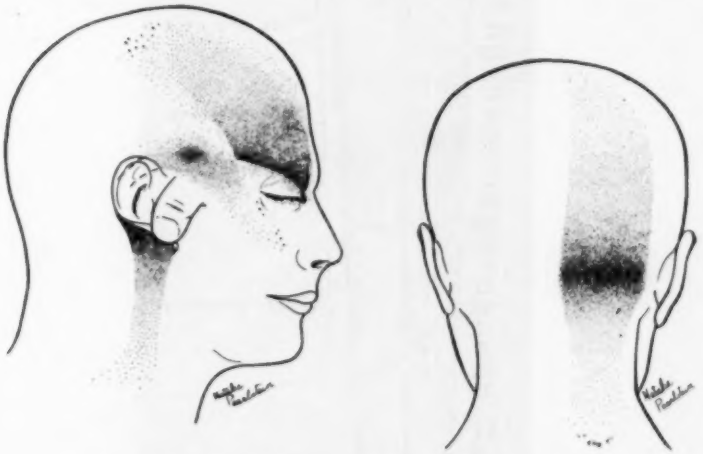

FIG. 1. (*Left*) Facial pain in cervical discopathy.
FIG. 2. (*Right*) Occipital headache in cervical discopathy.

Pains are often experienced in the occipital region (figure 2), suggesting, mistakenly, neuralgia of the great occipital nerve, or a tumor in the posterior cranial fossa. From the occiput the pains may extend down the nuchal region or radiate upward toward the vertex of the skull and into the fronto-temporal regions. In many cases there is tenderness on pressure over the areas of pain and over the arteries of the neck and the head.

Facial pain in cervical discopathy is frequently confused with both idiopathic and symptomatic neuralgia, with pains due to lesions of the dura mater or the dural venous sinuses, with the postconcussion syndrome and, above all, with migraine. (In both migraine and trigeminal neuralgia the pain is intermittent; in cervical discopathy it is constant.)

With regard to the seemingly atypical distribution of craniofacial pain in cervical discopathy, Ricard, Girard and Dupasquier [7] pointed out that topographically the pain corresponds to the fields of arterial distribution, particularly to the fields of the external carotid artery and its branches, such as the external maxillary (facial), lingual, occipital, postauricular, superficial temporal, internal maxillary and other arteries. The pain may be felt in the area of one or more of the branches of the external carotid artery.

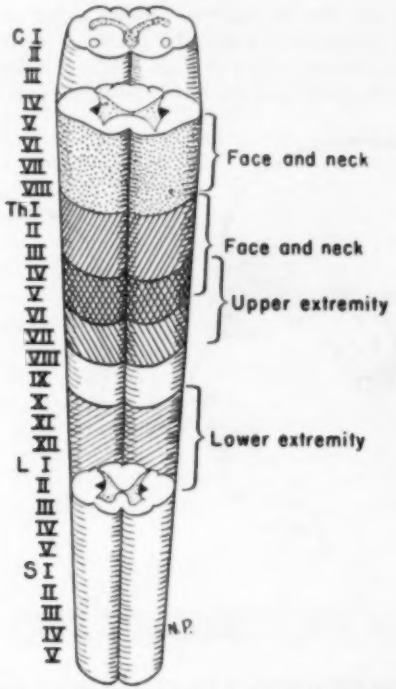

FIG. 3. Schematic drawing showing disposition of sympathetic gray matter in the spinal cord.

The mechanism of facial pain and headache in cervical discopathy and the distribution of the pain along arterial channels of the face and the scalp are best explained by the recent anatomic findings in the autonomic nervous system by Laruelle,[10] Guerrier [11] and Delmas, Laux and Guerrier.[12] Briefly stated, ventral nerve roots C5, C6, C7, C8 and T1 contain sympathetic fibers, a number of which reach, via the carotid plexus, the external carotid artery and the vessels arising from it.

Since Gaskell [13] and Langley,[14] it has been a fundamental tenet that the cells of origin of the preganglionic fibers of the sympathetic nervous system

are found only in the T2–L2 segments of the spinal cord, and that there are no white rami communicantes beyond these limits. But Laruelle [10] demonstrated the presence of sympathetic centers also in the mediolateral gray matter of the cervical cord at levels C5, C6, C7 and C8 (figure 3) which give rise to preganglionic fibers (white rami communicantes). These fibers,

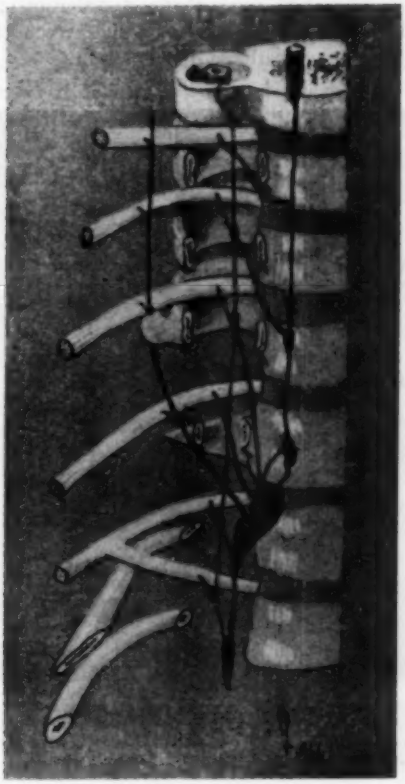

FIG. 4. The three cervical sympathetic chains and the vertebral nerves. (Courtesy of Yves Guerrier, Montpellier, France.)

emerging from the cord in the ventral roots, establish, in part, synaptic contact with postganglionic neurons in the small ganglia of a deep sympathetic chain that was discovered by Delmas, Laux and Guerrier [12] (figures 4 and 5). The deep chain consists of a tangled web of sympathetic fibers and small ganglionic masses that follow the vertebral artery along its course in the transverse foramina from C4 to C7. The deep ganglionic chain repre-

sents the peripheral relay station of the vasomotor sympathetic outflow, giving origin to postganglionic fibers which mediate vasoconstriction.

According to Tinel,[15] the fifth cervical root contains sympathetic fibers that join the carotid plexus, furnishing sympathetic innervation to the arteries of the neck and the head (cephalic sympathetic distribution); the sympathetic fibers in the sixth cervical root proceed to the subclavian artery and the brachial plexus (brachial sympathetic distribution); the sympathetic fibers in the seventh root are connected with the cardioaortic plexus and the phrenic nerves (thoracic sympathetic distribution).

FIG. 5. Section through the lower cervical region, presenting the arrangement of the three cervical sympathetic chains (a, b, c) and the vertebral nerves (1, 2). a. Deep sympathetic chain. b. Superficial collateral sympathetic chain. c. Classic sympathetic trunk. (Courtesy of Yves Guerrier.)

These anatomic findings explain why root involvement in cervical discopathy may cause preganglionic sympathetic irritation or overactivity. This can produce vasomotor disturbances in certain arterial areas, with resulting headaches and craniofacial pains; dysesthesias and vascular pains in the upper extremities, and, finally, anterior chest pains simulating angina pectoris. Involvement of the somatic sensory and motor fibers would produce symptoms and signs solely in their own areas of distribution. Additional sensory and motor phenomena appear in cord compression. The

illustration (figure 6) of Tinel [15] aptly demonstrates the topography of the sympathetic syndromes in cervical root involvement.

Treatment

Stretching of the cervical spine by means of traction is the most effective single therapeutic procedure in the treatment of both acute and chronic cases of cervical discopathy. Vertebral traction widens the intervertebral spaces and the intervertebral foramina; stretches the ligaments and joint capsules connected with the cervical spine; stretches muscles relieving muscle spasm; promotes the return of displaced disks and vertebrae to their original site, and facilitates reduction of subluxated apophyseal joints. The pressure exerted upon the nerve root, the blood vessels and the lymphatics is removed, with consequent relief of pain and restoration of normal circulation. Stretch-

Fig. 6. Topography of cervical sympathetic root syndromes. 1. Sternocervico-facial type. 2. Pectoroscapulo-superior brachial type. 3. Costoaxillo-inferior brachial type. (Jules Tinel, Courtesy of Masson & Cie, Paris.)

ing of the cervical spine aims at restoring anatomical relations and function to pre-disease level.

It is fortunate that traction alone is often sufficient to deal adequately with cervical discopathy. In acute and subacute cases continuous traction is employed, either in the hospital or in the patient's home. The traction force should be gradually increased, but not to such extent as to cause discomfort or aggravate the condition.

In chronic cases of cervical discopathy, or in patients for whom continuous traction is not practicable, intermittent traction is advisable. Short periods of traction carried out in the physician's office are combined with home traction performed daily over varying periods of time.[16]

Traction should be carried out with great care, to avoid damage to the vertebral articulations or increasing disk protrusion. For the same reason, vigorous exercises and manipulations involving the head and the neck should not be performed on a patient receiving traction.

In cases in which adequate trial with physical measures effects no relief, or when cord compression is either present or imminent, neurosurgical inter-

vention with either simple decompression or removal of the offending disk may be necessary. Diagnosis, alone, of cervical discopathy does not necessarily indicate the necessity for surgery. Most cases respond to "conservative" treatment. Furthermore, operative results in chronic cases are not always satisfactory. Osteoarthritic changes indicate Nature's attempt at healing and speak against surgical intervention.

Therapeutic Results

Table 1 shows the therapeutic results achieved in a series of 47 patients suffering from headaches and/or craniofacial pains who were treated with 742 sessions of traction applied by headsling to the cervical spine. Examination (including routine roentgenologic and occasional myelographic studies) disclosed cervical discopathy in 43 of the patients. The ages of the patients, 30 of whom were men, ranged from 19 to 58.

Table I

Number of patients	47
Recovered or much improved	33 (70%)
Improved	7 (15%)
Not benefited	7 (15%)

Not infrequently a patient improved after one to three treatments; usually, however, the progress was more gradual. The pain disappears first; the other sympathetic manifestations usually persist longer, but eventually they also become less pronounced and finally vanish.

Table II

	Disk Protrusion 14 (30%)	Discoösteophytic Lesions 29 (62%)	Discopathy Not Found 4 (7%)
Recovered or much improved	8 (57%)	22 (76%)	3 (75%)
Improved	2 (14%)	4 (14%)	1 (25%)
Not benefited	4 (28%)	3 (10%)	0

Routine roentgenograms and other methods of examination (myelography in 11 cases) revealed disk protrusion in 14 patients and discoösteophytic lesions in 29. Examination failed to disclose discopathy in four patients.

It has not been observed that treatment of cervical discopathy by vertebral traction is more effective when given early in the course of the disease.

Table III

	Recent Cases (3 to 6 Months)		Complaints Present Over One Year
Number of patients	12	25	10
Benefited	66%	70%	69%

Summary and Conclusions

1. The sympathetic nervous system plays a rôle in the mechanism of headaches and facial pains that occur in cervical discopathy.

2. In cervical discopathy, headaches and/or facial pains may arise through irritation of or pressure exerted upon cervical spinal roots, which contain not only somatic sensory (dorsal root) and motor fibers (ventral root) but also sympathetic fibers (ventral root). The craniofacial pains occur in sympathetic areas, especially in the distribution of the external carotid artery and its branches, to which arterial channels the preganglionic irritation caused by pathologic lesions of the cervical spine is transmitted. This elicits vasomotor reactions (vasoconstriction) which produce pain (sympathicogenetic pain).*

3. Stretching of the cervical spine by means of traction is therapeutically effective in most cases of craniofacial pain observed in cervical discopathy.

4. In all cases of headache and craniofacial pain of obscure origin, the cervical spine should be at least roentgenologically explored. It should be borne in mind, however, that absence of roentgenologic as well as myelographic evidence does not rule out discopathy.

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* It has not as yet been ascertained whether the sympathicogenetic pain travels through the habitual sensory channels or along the sympathetic nervous pathways (true sympathalgia).

SOME OBSERVATIONS UPON THE MIDDLEBROOK-DUBOS HEMAGGLUTINATION TEST IN MAN AND ANIMALS*

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THE Middlebrook-DuBos test for measurement of circulating hemagglutinins in the sera of tuberculous humans was initially described as a useful tool to aid the clinician in the diagnosis and management of the disease.[1, 2] Some reports have indicated that there was practical value in its common usage.[3, 4] Other reports have suggested that the test was not of great worth.[5, 6] Because some confusion still exists concerning the practical usefulness of the hemagglutination test in the field of tuberculosis, this report describes further observations upon it in man and animals.

METHODS

The hemagglutination test was performed substantially by the method originally described by Middlebrook, with a few modifications.[1, 3] Lederle's four-times-concentrated old tuberculin was used initially as the antigen. With each new vial received, overlapping controls were run with the old. At the suggestion of Dr. Middlebrook, Fraction 1A of the concentrated tuberculin was used exclusively after the first year.[7] All sheep red blood cells were secured from the same animal. Only macroscopic readings of agglutination or no agglutination were recorded, and all tubes were interpreted by at least two observers who had no knowledge of the identity of the serum. Two sera, one positive of known titer, were used as controls for each series of tests. Inactivation of serum was done at both 56° and 60° C., the latter proving better. Unadsorbed human group O red blood

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Concentrated tuberculin used in all tests was generously supplied by Dr. H. D. Piersma, Lederle Laboratories, Pearl River, New York.

Valuable aid and advice in these studies were given by Miss Winifred Osborne, Department of Bacteriology. Some of the sera studied were from patients of Dr. Stanley Lincoln, Biggs Memorial Hospital, Ithaca, New York. His coöperation is greatly appreciated.

Portions of this work have been presented at the Eastern Section meeting of the American College of Physicians, October, 1950, Rochester, New York, and at the Eastern Section meeting of the American Trudeau Society, November, 1951, Hartford, Connecticut.

cells were substituted for sheep cells on a few occasions, but were eliminated from use because lower titers than those with sheep cells commonly occurred.

Human sera came from two sources. The first was from 428 consecutive hospital admissions to the medical services in three hospitals.* The patients were tested for circulating hemagglutinins before being skin tested with old tuberculin by the standard Mantoux method. Dilutions of old tuberculin, for the latter test, were 1:10,000 and 1:500. Final recording of results of the serologic tests, the skin test and the hospital diagnosis was made after completion of the serologic procedure, and after hospital discharge of the patient.

Blood from patients being treated in a sanatorium for active tuberculosis was the second source of sera. All types of pulmonary disease were represented in the group. A singular feature of the group was that their infections had been observed for many months and the course of each had been well recorded by clinical and roentgenographic observation.

Animal sera came from standard impure breeds of laboratory guinea pigs and rabbits. Blood from both animals was obtained by direct cardiac puncture. Guinea pigs were infected intraperitoneally with virulent human strain tubercle bacilli, and the rabbits were inoculated intraocularly with the same organism.*

Results

I. Results of Hemagglutination Test in Routine Hospital Admissions to the Medical Service: Table 1 summarizes the results of the hemagglutination test in 428 routine medical hospital admissions, of whom 66 (approximately

Table I

Hemagglutination Test in 428 Consecutive Hospital Admissions

Disease	Total Cases	No. Positive	% Positive
Active tuberculosis	33	28	85%
Inactive tuberculosis	24	8	33%
Non-tuberculous disease	362	182	50%
Extra-pulmonary tuberculosis	9	5*	56%
Total	428	223	52%

* Of the 4 with negative serology, 3 had proved active foci of tuberculosis.

15 per cent of the total) were found to have tuberculosis. Some of these 66 patients were known to be tuberculous at the time of hospitalization and were admitted for other medical problems.

Among the 428 patients, 223 (52 per cent) had a positive serologic test for circulating hemagglutinins. Of the 362 who were nontuberculous, 182 (50 per cent) had positive tests. Extrapulmonary tuberculosis (genitourinary, bone and joint or lymph node) was discovered in nine patients; in

* Hospitals: Memorial, Crouse-Irving and University, all in Syracuse, New York.

TABLE II

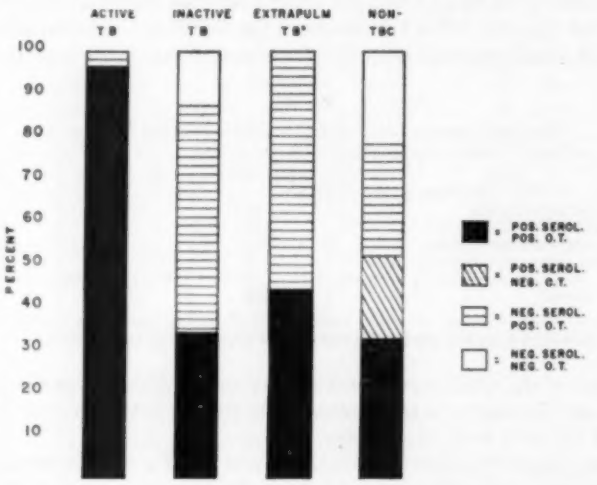
Titers of Hemagglutination Test

Disease	No. Cases	No. Positive	Range of Titers	% at or above 1:8	Mean
Active tuberculosis	33	26	1:2 to 1:64	77%	1:16
Inactive tuberculosis	24	7	1:4 to 1:64	71%	1:8
Extrapulmonary tuberculosis	9	5	1:2 to 1:16	80%	1:8
Nontuberculous disease	362	178	1:2 to 1:128	41%	1:8

seven it was active disease. Positive titers were found in only four of the nine. Twenty-eight of the 33 cases (85 per cent) with active pulmonary tuberculosis had positive titers.

Table 2 summarizes height of the hemagglutinin titers. The greatest mean titer (1:16) in the groups occurred in those with active pulmonary tuberculosis. The highest individual titer (1:128) was observed in a patient with nontuberculous disease. This individual, because of heart disease, was observed periodically for the next year, and he failed to show clinical evidences of tuberculosis; his last titer, measured eight months after the first, remained at the high level of 1:64.

Figure 1 correlates results between the hemagglutination test and the standard Mantoux test in the first 225 cases. In all categories more patients



* 7 OF 9 CASES (77.8%) IN THIS GROUP HAD CLINICALLY ACTIVE TUBERCULOSIS, ONE DIED SOON AFTER BEING TESTED

FIG. 1. Correlation between results in all cases (225) in whom both hemagglutination and tuberculin tests were performed.

had positive tuberculin reactions than positive hemagglutination titer. In the group with active tuberculosis, all had positive skin reactions to O.T. and 85 per cent had titers of agglutinins above 1:2. In the other groups, the skin test proved more indicative of previous tuberculous disease than the hemagglutination results.

Table 3 lists the diseases occurring in the 428 patients whose initial differential diagnosis included active pulmonary tuberculosis. The serologic test was positive in more than one-half the cases of both Hodgkin's lymphoma and bacterial (mostly pneumococcic) pneumonia. In most other disease categories, false-positive reactions were observed.

II. Results of Serial Hemagglutinin Titers Among a Small Series of Patients with Active Pulmonary Tuberculosis: Serial weekly hemagglutinin titers were measured in nine individuals with pulmonary tuberculosis. Figure 2 represents successive weekly determinations in six of the nine; the

TABLE III

Diseases Which Were Diagnostically Confusing with Tuberculosis

Disease	Serology	
	Positive	Negative
Hodgkin's disease	5	1
Carcinoma and other lung tumors	3	7
Lymphosarcoma	1	0
Sarcoidosis	1	0
Slowly resolving pneumonia	1	1
Lung abscess	0	0
Bacterial pneumonia	15	14
Bronchiectasis	1	4
Chronic fibrosis	4	5
Silicosis	0	1
Pyrexia (undetermined etiology)	0	3
Addison's disease	2	2
Pulmonary infarct	1	3
Total	34	41

curves of the remaining three patients could not be added without confusing the graph more. Patient 1 had advanced bilateral upper lobe cavity disease, treated for several months with streptomycin and para-aminosalicylic acid. The high titers (1:32–1:128) persisted throughout the period; his disease regressed during this time. Patient 2 had similar disease, was treated in a like fashion and was of the same approximate age. His disease progressed during the eight week period, and agglutinin determinations varied from 1:2 to 1:64. Patient 3, whose titers rose from 1:16 to 1:128 and then leveled at 1:64, also had advanced cavitary disease that progressed during the two months. Patient 4, whose titers ranged from high to low, had advanced disease that did not change in the two months and had not for the previous four. Patient 6 had moderately advanced disease which was clearing rapidly during the period of observation. At no time were his levels above 1:8. Patient 5 had acute disseminated miliary tuberculosis and meningitis. His

titers fell initially and subsequently rose to a moderate height. During the period he made rapid and gratifying clinical improvement.

In the total group of nine patients, tuberculosis became worse in three. In one, titers gradually rose to high levels (patient 3); in a second they varied considerably (patient 2), and in another, not diagrammed, they remained constant at medium levels. The one patient (case 5) with pulmonary and disseminated tuberculosis, in whom progress of the disease was eminently satisfactory, had hemagglutinin titers which fell initially and rose only to a moderate level of 1:16 thereafter. Titers of the patient (case 4)

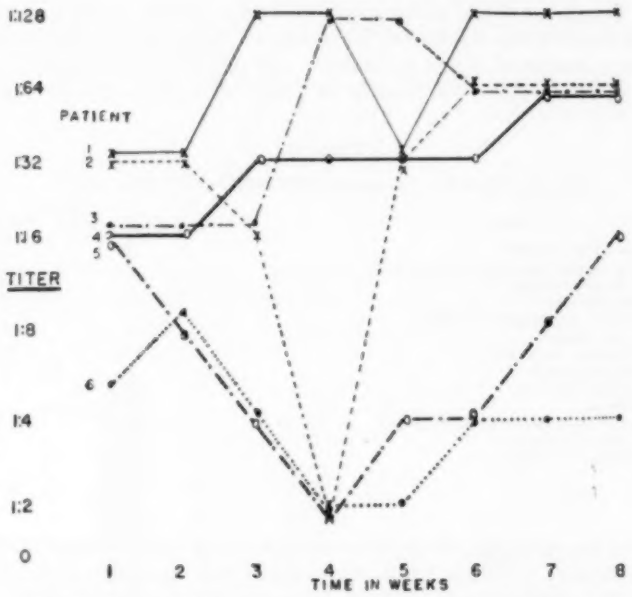


FIG. 2. Hemagglutination titers in patients with active tuberculosis.

whose disease remained stationary gradually rose from a moderate to a high level. Among the group of five in whom disease improved, weekly titers were recorded in all categories—rising (patient 1), falling, remaining constant at a low level (patient 6), and variable. At no time in any of the nine individuals were negative serologic tests titrated.

III. Results of Serial Hemagglutination Test in Guinea Pigs Infected Intraperitoneally with $H_{37}R_V$: Blood from 12 guinea pigs infected intraperitoneally with virulent human strain acid-fast bacilli was drawn weekly during the entire life of the animal. Two uninfected animals served as controls.

Figure 3 shows weekly titers in the 10 test animals and in the two controls. Serologic tests were negative at the end of the fourth week in all 12 animals, and at the end of the fifth week had remained negative in 10. Four animals at death had failed to develop circulating agglutinins. High titers of 1:128 were observed in only two animals, and in one of these the peak was present only in the blood drawn at death (case 3). The remaining four animals developed titers as high as 1:8 after from four to seven weeks. All animals died of acute disseminated tuberculosis, and all were acutely ill by the third week of illness.

IV. Results of Hemagglutination Studies in Rabbits Infected Intraocularly with $H_{37}R_V$: Serial hemagglutinin titers were measured in 48 rabbits for periods ranging for from two to eight months. Three rabbits were used

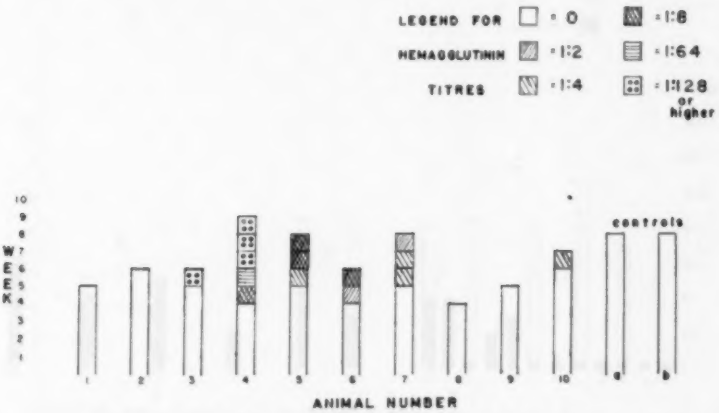


FIG. 3. Hemagglutination titers in tuberculous guinea pigs.

as controls; 11 rabbits were given 0.1 c.c. of 50 per cent old tuberculin in the flank; eight rabbits were infected intravenously with a sufficiently large dose of virulent human strain tubercle bacilli to assure the development of pulmonary lesions; 26 rabbits were infected intraocularly and developed advanced eye tuberculosis. Four of these received streptomycin for periods ranging for from four to eight weeks. Twenty others were treated with either adrenocorticotropic hormone or cortisone.[9]

Figure 4 summarizes the data upon two of the above groups; the three controls and the 11 who developed positive skin reactions to old tuberculin. No single titer in the control group was found above 1:8, but that level was observed at least twice in all three animals. All control rabbits had, at one time or another during the 29 week period, titers of 1:2 or 1:4, and generally such levels, once attained in an animal, persisted for several weeks.

Peak titers of 1:8 in a single animal, however, were never maintained for longer than two consecutive weeks. The first measurable titer was observed after the seventh week in one, and at the eighth or ninth week of the study period in the other two.

Two weeks after subcutaneous injection of old tuberculin, agglutinins developed in all animals. A sharp rise in their concentration to levels of 1:8 or above occurred. Thereafter, there was a continued rise to titers of 1:16 which, with very minor variations, were maintained. Measurements of titers after the fourth month were not routinely performed; rare periodic determinations during the subsequent four months suggested that the levels did not change. Four months was chosen as the arbitrary observation

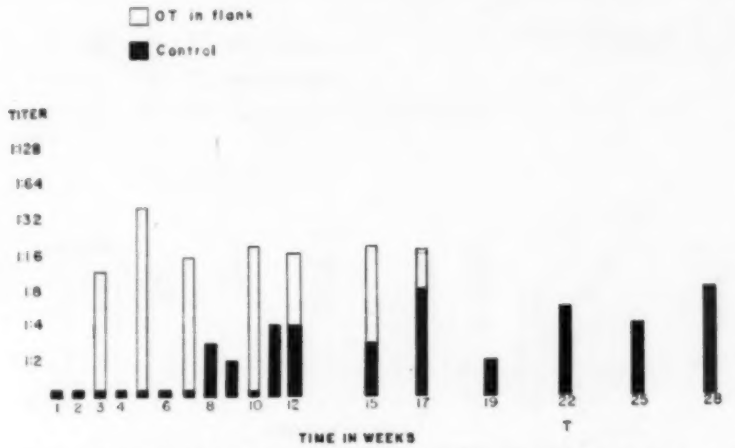


FIG. 4. Hemagglutination titers in normal and tuberculin sensitive rabbits. (Bars represent average of titers in three animals in the control group and of 11 animals in the tuberculin positive group.)

period for most animals; at that time a repeat tuberculin test was performed which interfered with interpretation of subsequent serial determinations. All animals tested at that time had positive skin reactions.

Figure 5 depicts hemagglutinin titers in the intravenously infected group of eight rabbits. No attempt was made to evaluate the results statistically; the scatter graph does, however, include all determinations made on these animals in the 28 week period. Four animals survived 28 weeks of observation; the others died of tuberculosis after four, five, seven and 12 weeks. Each animal was autopsied at the end of the observation period or at the time of death. In two of the eight, no disseminated tuberculous lesions were found. Tubercles in lungs, liver and spleen were seen in the other six. One of the two with no evident tuberculosis at death had the highest concen-

trations of agglutinins and was one of the first to develop measurable levels, a titer of 1:8 being found after the third week. He survived 12 weeks. The other animal failed to develop levels above 1:32 and generally, in the 28 week period of his life, levels averaged less than 1:16.

No predictable trend in the concentrations of the agglutinins from week to week was manifested; indeed, there were great variations in each animal. Those which developed the highest titers did not maintain them after the eleventh week.

In contrast to the unstable trend of the circulating hemagglutinins in disseminated types of rabbit tuberculosis, ocular tuberculosis, which was strictly localized, stimulated them in a more equable manner. Figure 6 is a scatter graph of individual determinations upon a series of eight rabbits infected

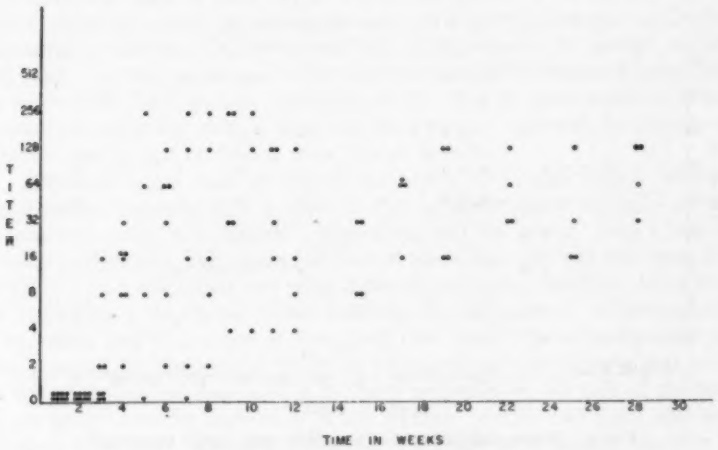


FIG. 5. Hemagglutination titers in rabbits infected with $H_{37}R_V$ intravenously.

intraocularly with tubercle bacilli. The majority failed to demonstrate hemagglutinins until the fifth week of infection. Thereafter, with few exceptions, titers rose to a higher average than 1:32, and remained more or less constantly at that level for seven months. In only four single instances was there a significant drop from average peak levels as time passed, and never was there a fall to levels below 1:8. The course of the ocular tuberculosis, as described previously, did not in any way parallel these levels. Peak of the optic disease was reached in two weeks, and by the end of the fifth to seventh week the tuberculosis had begun to organize.[8] At that time hemagglutinin titers were reaching their maximal concentration. At three months the disease was totally arrested, fibrotic and localized. Tubercle bacilli could not be recovered after the ninetieth day, and at autopsy tubercle bacilli in

lesions were rare. Therapy with streptomycin in this group and in those intravenously infected did not alter the advent or subsequent height of the titers.

Two of the rabbits shown in figure 6 whose ocular disease and hemagglutinin titers had been observed for six months were thereafter treated with adrenocorticotropic hormone. Bi-weekly determinations of agglutinins were continued for eight weeks. During exposure to adrenal hormone therapy, no change was noted in either the height of the titers or the disease itself. The two points noted at the thirty-first week in figure 6 represent the final titers in these two animals.

Eighteen other rabbits were infected intraocularly and treated with either cortisone (five animals) or adrenocorticotropic hormone (13 animals). Details of this study are reported elsewhere.[9] Despite the fact that the ocular

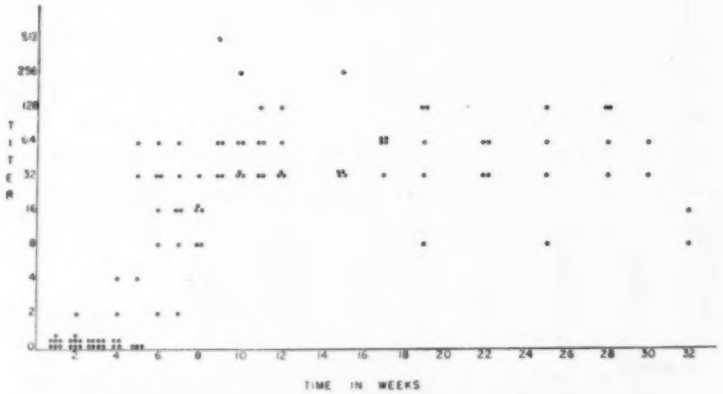


FIG. 6. Hemagglutination titers in rabbits with ocular tuberculosis.

disease was grossly different from that in the untreated animals, development of circulating hemagglutinins was not interrupted. During the third week of the disease they appeared and subsequently rose to levels ranging from 1:8 to 1:64 in all; no single level was ever higher. The rabbits universally developed disseminated tuberculosis, and most (14) were killed intentionally after 30 to 45 days' observation. In no single instance did height of titers for hemagglutinins suggest the ravaging, guinea pig-like disease that occurred.[9]

In the four animals allowed to survive, the titers, over the next six months, did not change from the levels attained after the fourth week. Although no other diagnostic tests were performed to measure regression of the miliary tuberculosis found early in the autopsied animals, the rabbits, after the second month, gained weight and appeared healthy in every way,

and it was presumed that they had successfully combated the disease; at least the original ocular lesions became fibrotic after cessation of hormonal therapy.[9]

Discussion

A new serologic test in the field of tuberculosis must fulfill at least two requirements prior to its general acceptance. It must be a dependable diagnostic tool and it must be useful as a method to predict and to measure accurately the course of the disease. The Middlebrook-DuBos hemagglutination test, as performed in this laboratory, does not have these qualifications.

There is no doubt that the animal with tuberculosis can develop circulating antibodies which presumably aid in his defense against the infection. There is little doubt that concentrations of certain of these antibodies may vary according to the stimulus that provokes them, or that they may wax and wane according to other vague factors that concern body health. There is also no question that the hemagglutination test of Middlebrook and DuBos measures at least one circulating antibody in the tuberculous animal, including man, and that when positive it indicates possible evidence of some type of tuberculosis, past, present, active or cured. But the mere presence of this measurable antibody cannot, from the observations reported, be considered either a specific test of disease or of disease activity.

Rothbard, in his study of approximately 400 individuals with or without tuberculosis, suggests that a titer of 1:8 is presumptive evidence of the presence of active tuberculosis.[4] Cummings and his group, using a technic similar to this, in a study upon 150 normal adults and children and upon 250 patients with tuberculosis and other diseases (sarcoid), conclude that a titer of 1:16 (his 1:32) is significant evidence for the presence of tuberculosis. They point out, in contrast to Rothbard, that there is little relationship between activity of disease and height of titers; at least they observe that there is not necessarily an appropriate antibody response on the part of the host to the progression or regression of the disease. Smith and Scott also emphasize, from their experiences with the test, that it "is usually negative in the far advanced type of case with poor prognosis and also in the patient with disease that has been arrested."[3] They conclude, as does Cummings, that the test is of little value for determining "clinical activity," and that in certain healthy individuals false-positive tests are observed. These conflicting reports point up the fact that there is, as yet, no practical proof of the specificity of the test in clinical tuberculosis.

Middlebrook, on the other hand, has insisted upon the high specificity of the reaction.[2] He further assumes that the "release of the antigen(s) which stimulates the production of the antibodies responsible for the hemagglutination reaction ceases soon after the bacilli stop multiplying."[2] It is evident from this that he believes a highly positive test can occur only in active tuberculosis, with its attendant presence of multiplying organisms. He presumes also that in lesions not associated with actively reproducing tubercle bacilli

there is no stimulus for the development or continuation of hemagglutinating antibodies. DuBos also believes that the height of a titer indicates the number of multiplying organisms within the host, i.e., the greater the number of multiplying organisms, the higher the titer.[10] None of these presumptions is substantiated by the present survey in two types of animal disease. At the time the tuberculous guinea pig becomes obviously ill, hemagglutination titers are at zero levels, and they do not reach measurable concentrations until very shortly before death (figure 3). A similar observation is made upon acute illness in rabbits (figure 5), in which the levels are so variable as to be uninterpretable. It is only in chronic localized disease of rabbits (figure 6) that the measurement of circulating hemagglutinins might assume some degree of immunologic importance, for in all infected animals the test becomes positive. For practical purposes, however, the level of the agglutinins in no way parallels the course of the disease. Indeed, they first appear after the peak intensity of the pathologic process has been passed, and become stabilized at high levels during the period when the eye disease is fibrosing. Though there is evidence that the antigen(s) responsible for the production of hemagglutinins is different from that responsible for a positive skin reaction to old tuberculin,[10] it is apparent that in the rabbit, at least, the agglutinins parallel the skin reactivity far more closely than they parallel eye disease. It cannot be absolutely true, therefore, that the circulating agglutinins die out rapidly as organisms disappear from tuberculous lesions. The test consequently cannot be used to measure the course of active tuberculosis.

In many other infectious diseases a certain small percentage of individuals may not respond with the development of antibodies as do the majority of the infected, e.g., syphilis and a positive complement fixation test. This occurs either because there is a diminished and often unexplained antibody production against the antigen involved, or because the test used is not specific. Middlebrook uses the former phenomenon to explain the imperfect results recorded with his test.[2] From our observations this explanation alone is not tenable. In the general population of a hospital ward, titers of 1:2 or higher are found in approximately 50 per cent of all medical cases (table 1). If a titer of 1:8 or higher is, arbitrarily, presumed to be a significant level, 40 per cent of the group have suggested tuberculosis (table 2).[4] By standard technics of roentgenology, laboratory analysis of sputum and other body secreta, and routine examinations, only 15 per cent of the same group have tuberculosis (table 1). False-positives in appreciable numbers (more than 25 per cent) are therefore found. Among the group of patients with proved active tuberculosis, 15 per cent have negative serologies. If the significant titer of 1:8 is used, over 20 per cent do not demonstrate a positive reaction (table 2). This number of false-negative reactions, together with the large number of false-positive reactions, precludes the use of the test as a dependable diagnostic tool. Furthermore, the test is of little

value as an aid in differential diagnosis of diseases that may be confused with tuberculosis (table 3).

With these three facts—frequent false-positive and false-negative reactions and a lack of specificity—the use of the hemagglutination test, performed by the presently accepted methods, can and should be discarded as a diagnostic instrument in clinical medicine. The skin reactivity to old tuberculin remains a more effective implement (figure 3).

Tubercle bacilli undoubtedly stimulate the production of hemagglutinins in the infected host. As measured, however, the presence or absence of these antibodies cannot, unfortunately, be used as a practicable guide in the clinical study of the disease. Although this test has proved to be impractical, there is still a great need for a serologic test that could be helpful to the clinician in his puzzling problems in the field of phthisiology.

Summary

1. As a diagnostic tool, the Middlebrook-DuBos hemagglutination test fails to be practicable. There are many false-positive and false-negative reactions in humans, and in a small series of cases it has been of no value as a differential diagnostic test.

2. The test fails to be of dependable value in determining the course of tuberculosis in humans and in animals with acute disease. In rabbits with optic disease, generally a chronic and localized infection, the titers do not parallel the course of the disease.

3. There continues to be a need for a dependable serologic test in the field of tuberculosis.

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GASTROINTESTINAL LESIONS OCCURRING IN UREMIA *

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THE occurrence of gastrointestinal lesions in uremia has long been recognized, but the comprehensive study of a large series of cases was not reported until the work of Jaffe and Laing appeared in 1934.[1] Prior to that time a number of articles had been written concerning the various types of lesions encountered in the digestive tract in uremia, with descriptions of the histologic changes observed in the lesions, and many theories were propounded to account for the alterations leading to necrosis, pseudomembrane formation and the development of so-called uremic ulcers; however, none of these reports, save that of Jaffe and Laing, was controlled by the study of a sufficiently large number of cases to render reliable their conclusions regarding the pathogenesis of the lesions. In the present study an attempt will be made to analyze the gastrointestinal lesions attributable to uremia in a large series of cases, to show the frequency of occurrence of the various alterations in different portions of the alimentary tract, to describe the pathologic histology of the lesions and to find the underlying changes which serve as a common denominator in the pathogenesis of the pseudomembranous and ulcerative lesions in uremia.

One of the earliest theories regarding the pathogenesis of uremic ulcers was proposed by Treitz in 1859.[2] His theory was that urea was excreted vicariously by the digestive tract in uremia and that the ammonium carbonate formed from the urea exerted an irritative and caustic action on the mucous membrane. The first dissention from this theory was expressed in 1890 by Hlava, who considered primary thrombosis of small vessels in the mucosa important in the production of ulceration.

In a series of 17 cases of uremia Fischer [3] in 1893 found ulcerations in the colon in four instances. Most of his cases showed swelling of the mucosa, with frequent mucosal hemorrhages, and in some there were superficial microscopic areas of necrosis. The submucosal blood vessels were dilated. Fischer observed the gastrointestinal inflammation and the hemorrhagic character of the lesions but did not explain the relations between the enterocolitis and renal insufficiency. He disagreed with Hlava, and considered thrombosis of vessels secondary to necrosis and ulceration in the digestive tract.

The importance of congestion of blood vessels and hemorrhage in the mucosa and submucosa was recognized also by Mathieu and Roux,[4] who in

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1902 expressed the opinion that such changes led to devitalization of the overlying tissue and thus allowed for infection and bacterial toxins to bring about necrosis and ulcer formation.

Pineau [5] concluded in his thesis in 1899 that at least three factors were acting together to produce the uremic necrotic and ulcerative lesions, namely, alterations of the blood vessels and perivascular tissue, irritation of nerves and increase of blood pressure. The importance of elevated blood pressure was later emphasized again by Bensaude, Cain and Antoine [6] in 1920 and by Lemierre in 1921. Jaffe found no correlation between the blood pressure level and the occurrence of uremic ulcers.

Siegmund [7] in 1929 described edema of the mucosa as the most common change in the intestinal tract in uremia, and concluded that the severe necrotizing lesions are not common. In four cases of uremia with necrosis and ulcer formation in the intestine he found arteriolonecrosis in the submucosa and considered this a primary alteration in the production of necrosis of the mucosa. The underlying renal lesions in his series were malignant nephrosclerosis in three cases and chronic glomerulonephritis in the fourth case.

In 1932 Würth [8] described his observations in three cases of uremia. He found focal necrosis and ulceration in the large intestine in one case of arteriolosclerotic kidney disease, and observed submucosal arteriolonecrosis. However, in two other instances he failed to find the necrotizing vascular changes in the submucosa, even in the presence of severe necrotic lesions in the alimentary canal, and for this reason was unable to confirm Siegmund's belief that arteriolonecrosis played a primary rôle in the pathogenesis of uremic ulcerations of the digestive tract. Würth preferred to accept the toxic theory.

Leyrat [9] in his thesis in 1933 concluded that azotemia is the direct cause of uremic ulcerations, and felt that urea should be considered the substance responsible for their production. He also regarded the gastrointestinal ulcerations as pathognomonic of uremia, as are albuminuric retinitis or pericarditis.

Streicher [10] in 1928 was able to produce marked gastroenteritis in dogs with one or both kidneys functioning by the intravenous administration of 10 per cent and 20 per cent urea solutions, 200 c.c. daily, given slowly by drip method for three days. A syndrome resembling uremia developed progressively during the urea administration, terminating with convulsions, bloody diarrhea, coma and death after 500 to 600 c.c. of urea solution had been injected. Autopsies performed on all animals revealed injection and hyperemia of the entire gastrointestinal tract, but no necrosis or ulceration was described. Histologic examination of tissues was reported as revealing gastrointestinal inflammation. Photographic illustration of the enteritis, which was described as congestion of the mucosa, was later interpreted by Jaffe as appearing hemorrhagic rather than congested.

Bollman and Mann in 1927 [11] studied the nitrogenous constituents of the blood in dogs following transplantation of ureters into different levels of the intestine, and observed marked elevation in blood urea without an increase in other nitrogenous substances in those animals having no kidney disease. Their animals survived 14 to 20 days and showed no evidence of uremia until the terminal one to two days, preceding which the blood urea levels decreased considerably. Necropsy of the dogs revealed hemorrhagic lesions in the stomach similar to those found in cases of uremia. No pseudomembranous or ulcerative lesions were found. In a discussion of this work Hench stated that these experiments afforded additional evidence that urea is practically a nontoxic substance, and expressed the opinion that, in the presence of such an intense "local uremia" as should be existent in the intestinal mucosa under the conditions of these experiments, one would expect the development of lesions in the gastrointestinal tract sooner than anywhere else. This work has not been followed up with a study of the effects of selective retention of urea on the kidneys, intestines, bone marrow, heart, etc.

Myerson [12] in 1927 observed manifestations of uremia in the pharynx, larynx, trachea and bronchi, and reported his clinical findings in 11 cases of uremia showing a peculiar dough-like coating on the mucous membranes of these parts. He found the membranous lesion during the stage of onset of uremia, and felt that when seen early this finding may be considered diagnostic of impending uremia.

A review of uremic stomatitis was presented by Hempstead and Hench [13] in 1930, in which Barie's classification of such lesions was outlined. Barie described an erythemopultaceous type of stomatitis consisting of a thick, gray, gluey pseudomembranous exudate superimposed upon a thickened, dry, red and distorted buccal mucosa. In addition, he observed an ulcerative form of lesion occurring on the gums, soft palate, faucial isthmus, tonsils, posterior surface of pharynx and on the buccal surface, presenting a redness of the mucosa covered by a pultaceous coat with superficial or deep ulceration of the mucosa. These ulcers were described as being painful to touch and with only slight bleeding tendency in some. Dalche and Claude in 1903 reported exudation and ulceration of the mucosa of the mouth in a case of chronic sclerotic nephritis with uremic purpura, and hemorrhagic ulcerations of the skin, umbilicus and anal mucosa. They thought the ulcers formed secondary to submucosal hemorrhage. Hempstead and Hench included in their report observations on four cases of definite uremic stomatitis which they found in over 300 cases of uremia. One case showed the erythemopultaceous type of stomatitis, while the other three were instances of the ulcerative type of lesion. All four cases had very high blood urea levels, and the salivary urea in three instances was proportionately elevated. Microscopic sections of the lesions revealed the tops of the papillary bodies to the extent that only the tips of the rete pegs remained in some. There were moderate leukocytic migration through the vessels of the papillary

body and occasional thrombosis of the vessels in the submucosa, with evidences of endothelial proliferation. An exudate on the surface contained abundant bacteria, but no distinct cellular structure could be recognized. The authors believed the lesions were related to the underlying nephritis and uremia and reviewed the theories regarding the pathogenesis involved, but offered no specific explanation for the process. In experimental acute uremia in dogs, stomatitis was not observed by Hench and Aldrich, and they suggested that a more chronic uremia may be required to produce stomatitis.

Bereston and Keil [14] (1941) reported ulcerative stomatitis in one case of uremia in which the lesions were located on the tongue surface, on the floor of the mouth and on the buccal surface of the gingiva. The lesions were painful and there was a pseudomembrane which could be lifted easily, leaving a raw, bleeding, superficially eroded area. A necropsy specimen taken from the inferior surface of the tongue revealed extensive necrosis of the mucosa, an exudate composed of necrotic epithelium, fibrin, degenerating polymorphonuclear leukocytes and clumps of bacteria. The submucosa appeared edematous and contained a cellular exudate, while the subjacent muscle layers revealed edema of the muscle bundles, cloudy swelling and haziness of the cross striations, occasional loss of striations with fragmentation of bundles, and irregular atrophy of muscle bundles with replacement fibrosis and occasional proliferation of sarcolemma nuclei. The muscle bundle changes were attributed to a diffusion of "toxins," since there was no evidence of primary vascular closure to account for the changes. The authors believed the localization of lesions on the inferior surface of the tongue and on the floor of the mouth resulted from the growth of local flora or accumulation of toxic products. Ulcerative lesions were not found in the remainder of the gastrointestinal tract in this case.

In a comprehensive report of the pathologic anatomic changes observed in 136 cases of uremia, Jaffe and Laing in 1934 described mild forms of intestinal changes in 27 per cent of cases, showing edema and mild hemorrhages in the mucosa and submucosa, chiefly in the large intestine. They found hemorrhagic lesions varying from scattered petechiae to extensive hemorrhagic infarction of the mucosa in 52.9 per cent of their series. Pseudomembranous and ulcerative lesions occurred in 19.8 per cent of cases, and were observed most frequently in the lower small intestine, ileocecal region and colon. In the pseudomembranous state the mucosa appeared completely necrotic, with dense clouds of bacteria in the inner portion of the membrane under which were seen hemorrhage, varying degrees of inflammation and thrombosis of veins about the inflammatory areas. The uremic ulcers presented sloping edges and dirty gray brown bases composed of fibrinoid necrotic tissue and degenerating leukocytes. Hemorrhages in the floor and edges of these ulcers were quite marked. The authors found arteriolosclerosis in 13 and arteriolonecrosis in five of the 27 cases with pseudomembranous and ulcerative lesions, while there were no arteriolar

changes found in nine such instances. Vascular necrosis was observed to be always in close proximity to areas of necrosis of the mucosa, was never found in the hemorrhagic or congestive stages of uremic lesions and was always inflammatory in nature, in contrast to the bland fibrinoid necrosis of arterioles seen in the kidneys in arteriolonephrosclerosis. On the basis of these findings the authors could not support the explanation of Siegmund that primary arteriolar changes account for the development of uremic necrotic and ulcerative lesions. Since there was no correlation found between the urea level and the occurrence of necrotic and ulcerative changes, they felt that Treitz' theory of mucosal irritation from urea elimination through the gastrointestinal tract was not upheld. Neither did they find any relationship between the blood creatinine, uric acid, indican or CO_2 combining power levels and uremic ulcers. The occurrence of ulcers in the esophagus and particularly in the vagina in uremia was cited as further evidence against the urea excretion hypothesis. The hypertension theory was dismissed because, in their series, exceedingly high blood pressures did not seem to favor the development of ulcerations. A hypotension factor was not mentioned in the discussion.

It was noted that hemorrhagic changes were the most common findings in the digestive tract in uremia, and that hemorrhages were most marked in association with pseudomembranous and ulcerative lesions. Furthermore, since hemorrhages appeared most frequently in the stomach, ileum and colon, while ulcerative and necrotic lesions were most commonly found in the ileum and colon, it was felt that necrosis and ulceration developed in those hemorrhagic regions where bacteria are more prevalent.

In conclusion, the authors stated that uremic necrosis and ulceration in the digestive tract developed secondary to hemorrhages, as originally suggested by Mathieu and Roux [4] (1902), with loosening of the mucosal epithelium and decreased vitality of tissues, with subsequent bacterial infection of the hemorrhagic tissue leading to necrosis and ulceration. They believed the gastrointestinal hemorrhages to be related to the hemorrhagic diathesis which occurs in uremia, and cited evidence in favor of the explanation of this mechanism on the basis of increased capillary permeability occurring indirectly by way of vasomotor nerves, as against the autointoxication theory.

Review of Gastrointestinal Lesions in 265 Cases of Uremia

Material Studied: The material for the present study was obtained from the autopsy protocols of the Department of Pathologic Anatomy of the Mayo Clinic over the 20 year period 1923 through 1942. In order that there be little reasonable doubt that the cases included in this study definitely presented the findings of the uremic syndrome, only those cases were used which had developed a blood urea level of 200 mg. per cent and a blood creatinine level of 10 mg. per cent, or higher, and had terminated in clinical uremia.

A total of 265 such cases was found in this group, representing nearly twice as many cases as studied and reported in the only previous large series found in the literature. It was felt that a study of this proportion would provide interesting knowledge of the gastrointestinal lesions found in uremia, as well as of another lesion of this syndrome, fibrinous uremic pericarditis. Another significant feature developed with this study was the relation of the type of renal lesion causing uremia to the frequency of occurrence of gastrointestinal lesions. To provide further significance for the results of this review, a control group of 100 nonuremic postmortem cases was studied for the occurrence of ulcerative gastrointestinal lesions.

Description of Lesions Found: All types of abnormal changes in the gastrointestinal tract, from nasopharynx to rectum, both gross and microscopic, were noted. The degree of severity of lesions, from the less severe changes, such as edema of mucosa and submucosa, through progressively significant hemorrhagic lesions to ulcerative and necrotic lesions, was described and charted. In the majority of instances the gross description of lesions was supported by microscopic findings.

Hemorrhagic lesions predominated, and these varied from multiple petechial hemorrhages to ecchymoses, and marked hemorrhages from mucosa and submucosa were a frequent finding. These changes were most frequently noted in the esophagus, stomach, cecum, ascending colon and rectum. They were also noted often in the jejunum and ileum. A few instances of localized hemorrhages in Peyer's patches were seen. Definite areas of infarction in the mucosa and submucosa were found in only a few instances. Thrombosis of arterioles in association with these lesions was seen only rarely. In several instances gross blood was present in the stomach or small or large bowel, with petechial hemorrhage in the mucosa and submucosa the only morphologic change found.

Next in frequency of occurrence were ulcerative and necrotic lesions. When present, these were usually in association with hemorrhagic lesions, and thus were most commonly found in the esophagus, stomach, cecum, ascending colon and rectum. A few ulcerative lesions were found in the jejunum and ileum. Pseudomembranous necrotic lesions were found a few times in every part of the digestive tract from nasopharynx to rectum.

The ulcerative lesions varied from 2 mm. to 3 cm. in diameter, and were usually multiple. The larger ulcers had gray-green necrotic bases with punched-out margins. In a few instances there were puckering of the margins and overhanging of the mucosa at the ulcer margins. Microscopically, the ulcerative lesions presented the appearance of acute ulcers with fibrin and a few erythrocytes and polymorphonuclear leukocytes over the surface. The margins and bases usually presented hemorrhagic edema in the mucosa and submucosa, with numerous lymphocytes and a few polymorphonuclear leukocytes present. The necrotic bases consisted of cell débris and a fibrinous membrane with a few lymphocytes and polymorpho-

TABLE I

Changes in the Digestive Tract in Uremia

	Mason's Series 265 Cases	Jaffe's Series 136 Cases
Edema and congestion	50—18.9%	37—27.1%
Mild hemorrhage	10— 3.8%	38—27.9%
Moderate hemorrhage	26— 9.8%	22—16.2%
Marked hemorrhage	20— 7.5%	11— 8.0%
Ulcerative and necrotic lesions	52—19.6%	27—19.8%
No changes described	10—40.3%	0— 0%

nuclear leukocytes. Occasionally clumps of bacteria were seen. In a few instances the ulcerative lesions showed no inflammatory cellular reaction, but degenerated mucosal cells were present and were surrounded by areas of bluish discoloration. These may have represented ulcerative lesions secondary to vascular thrombosis and infarction.

DISCUSSION

Table 1 shows a comparison of the postmortem findings in the digestive tract in uremia in the present series and in the series of Jaffe and Laing [1] in 1934. There is close agreement in the statistical results in the two groups in the more pronounced pathologic lesions, especially in the ulcerative and necrotic lesions and in those with marked hemorrhage. The current author's group revealed the occurrence of ulcerative and necrotic lesions in 19.6 per cent of cases of uremia, while that of Jaffe and Laing revealed a 19.8 per cent occurrence. Marked hemorrhagic lesions appeared in 7.5 per cent of this author's series and in 8 per cent of Jaffe's series. Edema and less

TABLE II

Relation of Type of Renal Lesion Causing Uremia and Incidence of Ulcerative and Pseudomembranous Gastrointestinal Lesions

Type of Renal Lesion	Number of Cases	Cases with Ulcer or Necrosis	Per Cent
Arteriolosclerosis	30	8	26.6
Arteriosclerosis	14	4	28.5
Chronic glomerulonephritis	62	14	22.6
Acute glomerulonephritis	29	4	13.8
Pyelonephritis	63	9	14.3
Embolic nephritis	4	0	
Suppurative nephritis	3	1	
Renal tuberculosis	4	1	
Renal abscesses—multiple	1	1	
Periarteritis nodosa	1	0	
Toxic nephritis	2	0	
Hydronephrosis	35	8	22.8
Polycystic kidney	6	1	
Postoperative anuria	13	1	
Nephrolithiasis	7	2	
Thrombosis renal vein	3	0	
Essential hypertension	4	0	
Cardiac failure	2	0	

severe hemorrhagic lesions were described more frequently by Jaffe than by this author. No pathologic alterations were noted in the gastrointestinal tract in 40.3 per cent of cases in the present series, while Jaffe reported changes in all of his cases. It is in the minor changes, such as edema and mild hemorrhagic lesions, that this discrepancy occurs between the two series.

Table 2 is arranged in an attempt to show the possible relation between the type of renal lesion causing uremia and the incidence of ulcerative and necrotic pseudomembranous gastrointestinal lesions. Those renal diseases associated with extensive degenerative vascular changes in the body appear to be the ones most commonly accompanied by ulcer formation and necrosis in the presence of uremia. This observation is in keeping with the pathologic evidence that hemorrhage and vascular lesions are the chief common denominators in the pathogenesis of severe gastrointestinal lesions in uremia. Although many of the less frequently encountered renal lesions in this series are too small in number to be of any statistical value, they are nevertheless shown in the table for comparison.

TABLE III

Uremia and Age Incidence of Ulcerative-Necrotic Gastrointestinal Lesions and Pericarditis

Age Group	Number of Cases with Blood Urea 200 mg. % and Creatinine 10 mg. %	Cases with Ulcerative and Necrotic Gastrointestinal Lesions	Cases with Fibrinous "Uremic" Pericarditis
0–20 years	29	9—13.0%	6—26.1%
21–40 years	71	15—21.1%	21—29.6%
41–60 years	182	20—19.6%	22—21.6%
61–80 years	69	14—20.9%	4—20.0%
Total Cases	265	52—19.6%	53—20.0%

Table 3 indicates the age incidence of ulcerative and necrotic gastrointestinal lesions in uremia and of fibrinous "uremic" pericarditis, a severe lesion involving another system in the uremic syndrome. It is interesting to note that the severe gastrointestinal lesions occur appreciably less frequently in the one to 20 year age group, while the severe pericardial lesion develops less often in the 60 to 80 year age group. The percentage occurrence of these two lesions for the group as a whole is very nearly the same. Further analysis of the cases reveals, however, that of the 53 instances of "uremic" pericarditis, only 37.8 per cent occurred in cases with ulcerative gastrointestinal lesions, while 62.2 per cent occurred in cases without severe alimentary tract lesions. Although in this study no further attempt was made to explain the pathogenesis of "uremic" pericarditis, there is perhaps an inference that it is not based on vascular and hemorrhagic phenomena, as the gastrointestinal lesions appear to be.

Control Cases: It has often been shown that unexplained ulcerative lesions of the gastrointestinal tract are found at postmortem examination in

disease states other than uremia. For the purpose of determining the frequency of such findings the postmortem protocols of 100 cases without uremia or elevation of non-protein nitrogen were reviewed. Disease states known to be sometimes associated with ulcerative alimentary tract lesions, such as extensive burns, jaundice, increased intracranial pressure, etc., were excluded from this control series.

Ten of the 100 cases studied presented acute ulcerative gastrointestinal lesions varying from superficial, small mucosal ulcerations with surrounding inflammatory reaction to multiple, well developed ulcers and necrotic pseudomembrane formation. The major pathologic difference between these lesions and those occurring in uremia was that hemorrhage and edema in the mucosa and submucosa were more pronounced in the cases with uremia.

Summary and Conclusions

1. Pathologic anatomic alterations occur in the gastrointestinal tract in 60 per cent of cases of uremia.

2. Edema and varying degrees of hemorrhage into the mucosa and submucosa are the changes most frequently found, and constitute the predominant common denominator finding in the cases with ulcerative and necrotic lesions of the alimentary tract.

3. Ulcerative and pseudomembranous necrotic lesions are present in the gastrointestinal tract in 19.6 per cent of cases of uremia.

4. Renal diseases associated with extensive degenerative vascular changes in the body, such as arterionephrosclerosis, arteriolonephrosclerosis and chronic glomerulonephritis, appear to be more commonly accompanied by gastrointestinal hemorrhagic phenomena, mucosal and submucosal necrosis and ulcer formation.

5. Uremic ulcers and uremic pericarditis occur with the same frequency for the group as a whole. The gastrointestinal lesions occur less often in the age group one to 20 years, while pericarditis develops less often in the age group 60 to 80 years. Uremic pericarditis is found about 25 per cent more often not associated with ulcerative gastrointestinal lesions than in company with such lesions.

6. Ten per cent of 100 control cases without uremia or elevated nonprotein nitrogen present acute ulcerative gastrointestinal lesions, varying from superficial ulcerations with surrounding inflammatory reaction to well developed ulcers and necrotic pseudomembrane formation. Pathologically, there is less hemorrhagic character to these lesions than to the ulcerative lesions seen in uremia.

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WHAT IS THE MODE OF ACTION OF THIOCYANATE COMPOUNDS IN ESSENTIAL HYPERTENSION?*

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INTRODUCTION

ALTHOUGH the thiocyanate compounds have been used as remedies for essential hypertension since early in the Twentieth Century, our incomplete knowledge of their mode of action, and the variability of the clinical response, have served to throw doubt upon their therapeutic value. Evidence is accumulating, however, that the thiocyanate ion may have a specific action upon some of the glands of internal secretion, including the adrenal cortex. In view of the recent interest concerning the rôle of the adrenal cortex in the pathogenesis of essential hypertension,[1-7] it seems worth while to review what is already known, to present some unpublished clinical observations, and to consider further the implications of certain new experimental findings in regard to the clinical data.

PHARMACOLOGIC BACKGROUND

The term "thiocyanate," which is in current use, has various synonyms—sulfocyanate, sulfocyanide, thiocyanide and rhodanate. All refer to the anion -SCN, which is usually administered in the form of the sodium or potassium salt. We know that thiocyanate occurs normally in saliva, so that all of us swallow approximately 0.1 gm. a day. Ingested, thiocyanate is distributed throughout the extracellular fluid, and has been used as an index of its volume. Thiocyanate is excreted unchanged by the kidney. Excretion occurs slowly, and is not complete until two or three weeks after discontinuing the drug.

Claude Bernard demonstrated certain pharmacologic characteristics of thiocyanate to medical students in 1856.[8] Injected into the leg muscles or hearts of frogs, concentrated solutions of the drug produced muscular paralysis or cardiac arrest without interfering with nerve conduction. He concluded that thiocyanate destroyed muscular irritability, and wondered how such a toxic substance could exist in normal human saliva without causing accidents.

Nothing was known of the therapeutic uses of thiocyanate until 1903, when Pauli made a systematic survey of chemicals which might be useful in the field of medicine.[9] Of a series of common anions, he found that the

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thiocyanate ion exerted the maximal inhibitory effect on the precipitation of protein, next to it being the iodide and bromide ions. He reasoned that thiocyanate should exert therapeutic powers comparable in potency to iodides and bromides. He treated 35 patients with various nervous disorders, including cardiac neuroses and the menopausal syndrome, with a gram of sodium thiocyanate daily. This dose, which is considered large today, exerted a very satisfactory sedative action upon such symptoms as pain, vertigo, restlessness, headache, insomnia, irritability, fear and palpitation. In patients with hypertension he discovered a marked reduction in blood pressure, with relief of vertigo and other subjective symptoms. He noted various analogies between the action of iodides and thiocyanates.

Since Pauli's time, the clinical use of thiocyanate has been chiefly in patients with hypertension. In 1925 Nichols awakened interest in the use of thiocyanate in this country.[10] His paper, based on clinical and pharmacologic observations extending over 14 years, starts out with the statement:

"Personal experience for a number of years has convinced me that sodium sulphocyanate is one of the most efficacious remedies available for the treatment of hypertension."

He observed reductions of blood pressure of from 20 to 40 mm. appearing within a few weeks of the beginning of treatment. He commented on the gradual decline of blood pressure accompanied by relief of symptoms, and noted the late appearance of disagreeable side effects, which suggested to him an accumulation of the drug in the system. He administered 1 gm. a day, rather a large dose, for several weeks at a time until he obtained the desired effect, and continued to give it intermittently, either a week or two every month, or whenever blood pressure rose unduly, for as long as 12 years.

In 1928 Smith and Rudolf reported the effect of three different dosages of thiocyanate on a total of 72 hypertensive patients.[11] A gram a day produced a fall of 20 to 80 mm. systolic pressure, 36 hours to a week after starting the drug. Diastolic pressure fell less sharply. Weakness and fatigue were often pronounced, and persisted up to a week after the drug was withdrawn. During this period blood pressure might continue to fall, gradually returning to its former height in the next few weeks. Patients observed a diminution in tension and headache, disappearance of hot flushes, a lessening of nervousness and, sometimes, drowsiness. Those with insomnia could now sleep through the night. Normal subjects responded to the same dose with a fall in pressure, sometimes to under 100 mm., at which time the drug was stopped; they experienced no symptoms. In patients receiving 0.6 gm. or 0.3 gm. of the drug a day the reduction in blood pressure was more gradual, and did not begin until the second week of therapy. Weakness and fatigue were less common, although a few experienced slight lassitude. Clinical improvement was more variable.

During the decade following Nichols' paper, the initial popularity of thiocyanate was tempered by a number of reports on toxic manifestations

resulting from its use. Other investigators, who gave smaller doses, reported little or no toxicity and often no decrease in blood pressure. In 1936, Barker published a highly illuminating paper in which he disclosed the reason for many of the poor results of thiocyanate therapy.[12] He found that the renal excretion of thiocyanate varied greatly from patient to patient. In a patient whose excretion was rapid, a given dose might be wholly ineffective, whereas the same dose in a case where excretion was slow might have an excellent depressor effect. In some patients, the excretion might be so slow that the drug reached high blood levels and severe toxic effects would result. Barker showed that by individualizing the dosage through control of the blood thiocyanate level a satisfactory depressor effect could be obtained

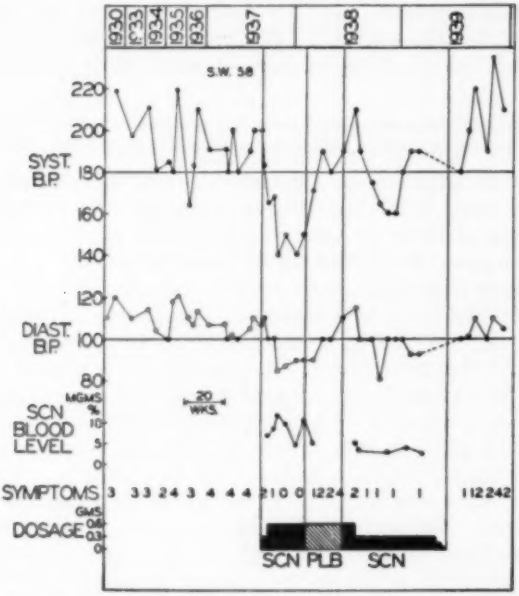


FIG. 1. S. W. Blood pressure levels and rating of severity of symptoms in a patient with essential hypertension while treated with thiocyanate and while taking a placebo. The blood levels of thiocyanate were relatively low; there were no toxic symptoms. Control observations were made in the Cardiac Clinic for over six months before thiocyanate was given. The following symptoms were specifically rated on each visit: headache, dyspnea on exertion, precordial pain, palpitation, nervousness. The symptoms were rated together; the score applies to the most conspicuous symptom or symptoms:

4 = severe,
3 = marked,
2 = moderate,
1 = slight,
0 = no symptoms whatsoever.

SCN = thiocyanate, PLB = placebo, Age = on entering study in 1937.

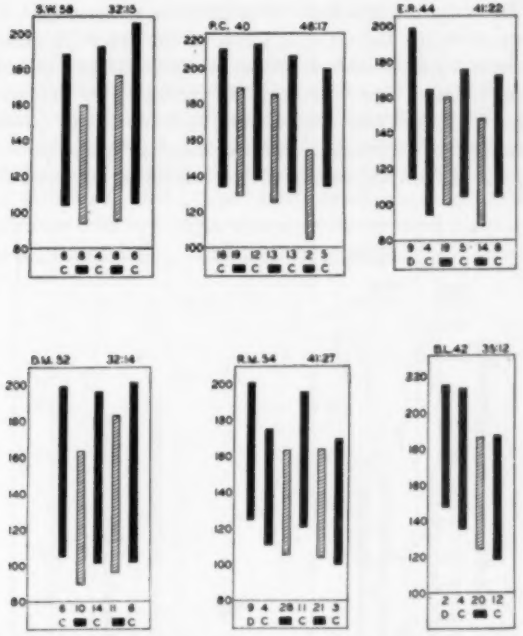


FIG. 2. The average blood pressures of six patients who responded well to thiocyanate therapy. The black columns indicate the average pressures during control periods, the cross-hatched columns, the average pressures during therapeutic periods. The first number in the upper right corner indicates *months* of observation in the Cardiac Clinic, the second number, *total months* of thiocyanate therapy, divided into one, two or three courses. Systolic pressure = top of column. Diastolic pressure = bottom of column. Number of blood pressures (obtained on different days) *averaged* is shown below each column.

D = observations in general dispensary.
C = control period in Cardiac Clinic.
■ = therapeutic period.

and most of the disturbing toxic effects avoided. He found the optimal range of thiocyanate in the blood to lie between 8 and 12 mg. per cent.

CLINICAL OBSERVATIONS *

Shortly after the appearance of Barker's paper, I began the study of a group of patients with hypertension who were treated with thiocyanate

* These studies were referred to in talks on thiocyanate therapy during a Postgraduate Course on Arterial Hypertension of the American College of Physicians on March 14, 1939, and before the Baltimore City Medical Society on January 19, 1940. They were summarized and presented before the Johns Hopkins Medical Alumni Association on February 23, 1940. Further observations and plans for publication were interrupted by the closing of the Cardiac Clinic in 1941 because of World War II. I have subsequently used the drug in 50 or 60 additional private and dispensary patients, with similar results.

while blood levels were controlled. The group was composed of 19 ambulatory patients attending the Cardiac Clinic of the Johns Hopkins Hospital; they were seen every three or four weeks or oftener over a period of from a year and a half to four years. Most of the patients were colored women between the ages of 30 and 60. There were, however, three colored and two white men and one white woman. All had essential hypertension, two of the malignant type. Three had recovered from cerebral accidents before treat-

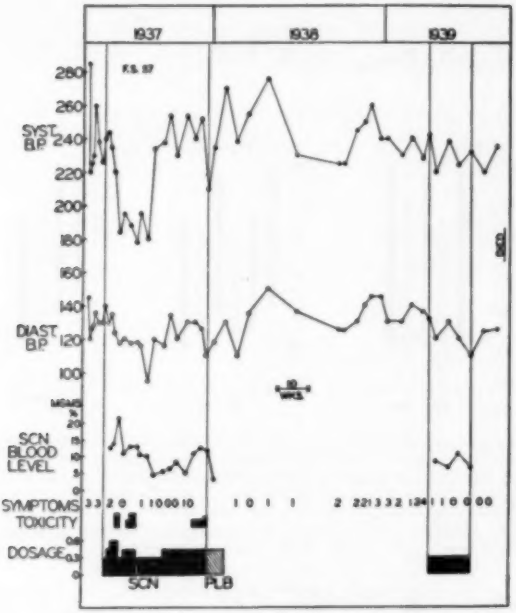


FIG. 3. F. S. Blood pressure levels and rating of severity of symptoms in a patient with essential hypertension treated with thiocyanate who developed symptoms of toxicity at high to optimal thiocyanate blood levels despite well marked clinical improvement, and whose blood pressure rose again when blood thiocyanate fell below the optimal range. Legends as in figure 1.

ment was started; two had anginal pain; one had had a splanchnicectomy three years previously. Usually the patients had previously been treated in the general dispensary over a period of months, during which time a number of blood pressure readings were recorded. Thiocyanate was not started, however, until several additional resting blood pressure measurements had been made over a period of from four to six weeks. All blood pressures were taken with the patient recumbent after at least 20 minutes' rest. Three or four successive blood pressures were taken at intervals of a

few minutes; the lowest one was recorded as the resting blood pressure for that day.

Potassium thiocyanate was then started, and the blood level was followed at weekly intervals during the next few weeks, and thereafter every three or four weeks, in order to maintain the desired blood level. The patients were usually started on 0.3 gm. a day; after approximately six weeks the dose was sometimes increased, and from then on the maintenance dose was adjusted by the blood level. Our maintenance doses over the course of years ranged from 0.15 to 1.3 gm. a day; the most usual maintenance dosage lay between 0.3 and 0.6 gm. Although infrequent, it was sometimes neces-

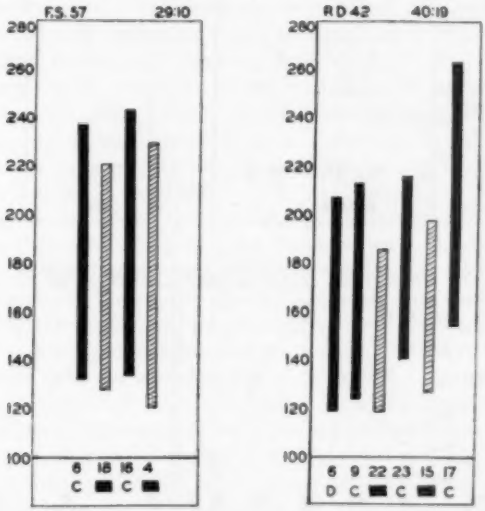


FIG. 4. The average blood pressures both with and without thiocyanate therapy of two patients with far advanced hypertension. Legends as in figure 2.

sary to change the dose from time to time in order to maintain the same blood level in a given patient. When possible, patients were given thiocyanate for a year and then observed for a year without the drug, to avoid possible seasonal effects on the blood pressure. Subsequent courses of thiocyanate were given to most of the patients so that the effects of the drug at different stages of the same disease process could be studied. Blood pressures were averaged for each therapeutic period and compared with the average pressures over similar periods of time when the patient was *not* receiving thiocyanate.

In general, the results of this study substantiated the work of Nichols,[10] Smith and Rudolf,[11] and Barker.[12] Fourteen of the 19 patients, or 74 per

cent, showed well marked drops in blood pressure. If the patient was started on small doses, the blood pressure did not fall to any extent for several weeks, or at about the time the blood level had reached 5 to 7 mg. per cent. The drop in systolic pressure was more marked than the fall in diastolic pressure. The blood pressure often dropped to unusually low levels over a period of several weeks when the blood level first reached a high figure, in the range of 10 to 14 mg. per cent. In most patients there was a high degree of correlation between the drop in blood pressure and the level of the thiocyanate in the blood. The blood pressure might remain low over a period of

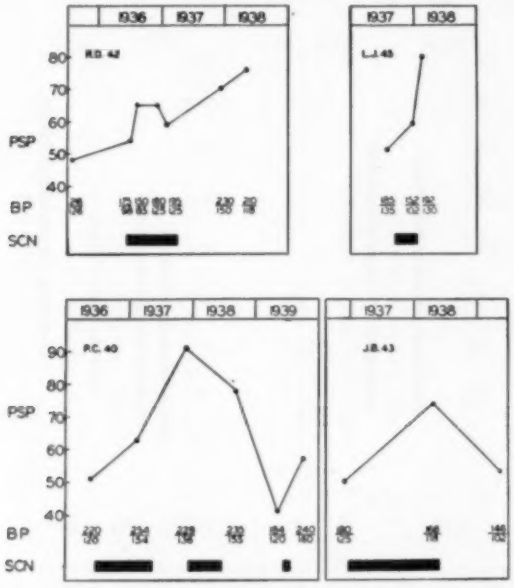


FIG. 5. Observations on the excretion of phenolsulfonphthalein before, during and after thiocyanate therapy in four patients with essential hypertension.

months, or escape after a period. Five of our patients showed little response to thiocyanate, which compared closely with the 22 per cent noted by Barker, Lindberg and Wald among 246 patients.[18] Of the 16 patients with symptoms of hypertension, all but two obtained marked symptomatic relief. Before treatment, five patients had severe symptoms, including excruciating headaches, nervousness, precordial pain and dyspnea, which were entirely relieved. Three, less severely affected, also became symptom free. Six others noted improvement in symptoms but were not well. Headache was the symptom most improved, but other symptoms were also ameli-

orated. Whereas not all patients reported perfect results, many stated that they "never felt better." Of the three patients who had never experienced symptoms, one had an average drop in systolic pressure of 40 mm.

A typical case showing a good response to the drug is illustrated in figure 1. S. W., a 58 year old colored woman who had suffered from headaches and had been known to have hypertension since 1930, complained of extreme nervousness, exhaustion, precordial aching, occasional dyspnea, paroxysmal headaches and dizziness. Her blood pressure was moderately high (200/100 mm. of Hg) and her heart somewhat enlarged. On thiocyanate her blood pressure, especially the systolic pressure, promptly fell and symptoms disappeared. On a placebo, her blood pressure mounted and symptoms recurred. A second course had much the same effect, although the lowered blood pressure was not maintained on a smaller dose of thiocyanate. Following the second course, symptoms again recurred.

The average blood pressures of six patients who were observed for several years both on and off the drug, and who responded well as to both a drop in blood pressure and improvement in symptoms, are shown in figure 2.* The first set of average pressures is on the patient S. W., whose detailed findings are shown in figure 1. The next patient, P. C., showed exceedingly good results during three different courses of thiocyanate. E. R. illustrates the difference which may be found between blood pressures obtained in a general dispensary and at rest in the Cardiac Clinic. The first course of thiocyanate therapy produced little more fall than had already occurred during the control period of study in the Cardiac Clinic. Blood pressure rose following discontinuance of therapy, however, and a further fall was obtained during a second course of treatment. The same phenomenon is seen in the patient R. M. The patient B. L. illustrates a fall in blood pressure when taking thiocyanate which was not followed by a rise when the drug was stopped; this was also seen in several other patients.

Figure 3 shows a patient, F. S., who had an initial drop in blood pressure which later rose abruptly as the blood thiocyanate level fell. Her blood pressure thereafter tended to escape from the effects of the drug, as did 25 per cent of the patients of Davis and Barker.[14]

F. S., a colored woman of 57, had arterial changes in the fundi four years before this study started. In 1935 her blood pressure was said to be 220. For years she had suffered from throbbing headaches over the vertex, and had noted increasing exertional dyspnea and orthopnea. For three months she occasionally felt quite severe substernal pain radiating to both shoulders and down the inside of both arms, precipitated by anxiety or eating, and lasting for from five minutes to an hour. If she walked two blocks she had to stop because of cramping pain in the muscles of the right calf.

* Six other patients showed similar results but, for various reasons, were not followed so long.

She was observed frequently for a month; her blood pressure remained constantly high. After thiocyanate was started she felt better in every way. At the end of two months she said, "I feel so much better than I did last year that I don't know what to do with myself." Precordial pain had gone, and she slept well and had no complaints. Because of symptoms of toxicity, however, the dosage was reduced, the thiocyanate blood level fell

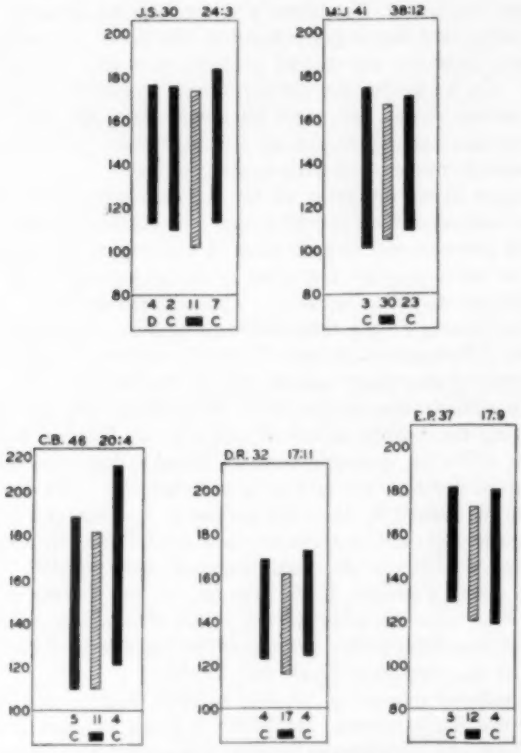


FIG. 6. The average blood pressure levels of five patients with essential hypertension who showed the least response to thiocyanate therapy. Legends as in figure 2.

and the systolic pressure rose sharply. An increase in dosage once again resulted in toxic symptoms, and the drug was stopped.

Six months later there was a gradual return of orthopnea and dyspnea. A year later, when she had had no thiocyanate for 15 months, there was a "constant misery" at the lower end of her sternum. These symptoms increased to a point where it was thought worth while to try thiocyanate again.

Eight days after starting it she had a mild cerebral accident, but the blood pressure was unaltered. Accordingly, the drug was continued, with a complete remission of symptoms for a second time, although the blood thiocyanate levels were low and the fall in blood pressure was trifling. The drug was stopped and she continued to feel well until two months later, when a sudden attack of pain followed eating, and she died at home within 24 hours, apparently of myocardial infarction. A summary of the blood pressure averages in the terminal years of her disease is shown in figure 4.

TABLE I

The Effect of Alternating Thiocyanate (SCN) Therapy and Control Periods over Three and One-Half Years
R. D. W. F. Born 1893—Essential Hypertension

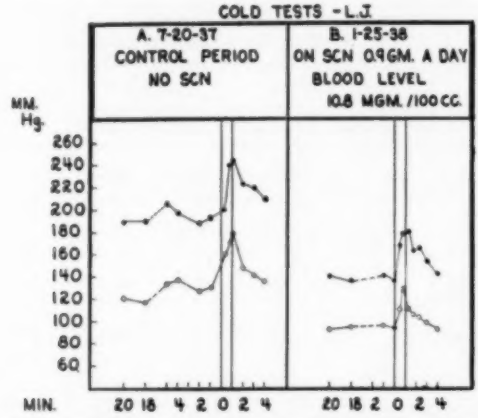
Period	Taking SCN	No. of Visits	Systolic		Diastolic		Symptoms	SCN Dose Gm.	Blood Level Mg.
			Average	Range	Average	Range			
July 1935 to June 1936	No	15	210.5	186–230	121.6	100–140	3	—	—
June 1936 to Sep. 1936	Yes	8	182.5	170–190	113.6	98–120	1	0.3 0.45	3–10
Sep. 1936 to Mar. 1937	Yes	14	186.5	176–200	121.8	110–135	1	0.45 0.6	9–21.5
Mar. 1937 to Sep. 1937	No	6	201.1	190–220	134.5	130–145	3	—	—
Sep. 1937 to Mar. 1938	No	6	218.8	200–230	142.5	130–155	3	—	—
Apr. 1938 H	No	11	222.4	200–240	127.8	110–138	2	—	—
May 1938 to Jan. 1939	Yes	15	197.3	175–220	126.6	115–140	1	0.3 0.45 0.3 0.15	7–18
Feb. 1939 H	No	17	262.4	210–300	154.9	120–180	4	—	—

The blood pressures are expressed in mm. Hg.
Symptoms: 4 = severe; 3 = marked; 2 = moderate; 1 = slight.
SCN = thiocyanate.
H = hospitalized.

Another patient studied late in the course of her illness was R. D., a white woman of 42, who was followed for a total of 40 months, or for over three years. During this time she took thiocyanate for 19 months, divided into two courses (figure 4 and table 1). Meanwhile, her basic blood pressure was rising and she died in heart failure shortly after the last blood pressure averages were made. Thiocyanate on both occasions produced a definite overall drop in blood pressure. During the first course, 0.6 gm. a day produced a blood level of 21 mg. per cent on one occasion without toxic symptoms, whereas during the last course a much smaller dose, 0.15 gm.,

produced a blood level of 13 mg. per cent *with* symptoms of toxicity. This decrease in tolerance to thiocyanate probably reflected progression in the underlying disease process, although at the time of these observations renal function was adequate.

The variations in her excretion of phenolsulfonphthalein during both thiocyanate therapy and control periods are shown in figure 5, together with similar observations on three of the other patients. All four showed a tendency toward improved excretion during the first course of therapy. In three patients (R. D., L. J. and P. C.), the improvement continued *after*



	SYST. B.P.	DIAST. B.P.	SYST. B.P.	DIAST. B.P.
RESTING	192	130	136	94
PEAK	242	178	180	128
RISE IN MM.	50	48	44	34
% INCREASE	26	37	32	36

FIG. 7. A comparison of two cold pressor tests performed on the same patient before and during thiocyanate therapy.

withdrawal of the drug and reached a conspicuously high level of excretion in contrast to the pretreatment level. The fourth patient, J. B., showed a return to the pretreatment level; at this time, in contrast to the others, his blood pressure was considerably reduced.

The average blood pressures of the five patients who showed the least response to thiocyanate therapy are shown in figure 6. All showed a minimal decrease of systolic and three of diastolic pressure. One, C. B., showed no change in the average diastolic pressure; another, M. J., showed a slight average diastolic *rise* over the period of a year. Comparison of the

average pressures of C. B. during the two control periods suggests that his basic blood pressure levels were rising, and that thiocyanate may have postponed the onset of this elevation.

Investigation of the vasomotor reactivity during the cold pressor test of patient L. J. both in a control period and while on thiocyanate therapy is shown in figure 7. Although the resting blood pressures at the time of the two tests were quite different, the rises of blood pressure while the hand was in ice water were very similar, indicating no marked tendency of thiocyanate to decrease the patient's hyperreactivity.

Discussion

Although the mode of action of thiocyanate in hypertension is usually referred to as a sedative effect[15] or a smooth muscle depressant,[16, 17] with the implication that blood pressure lowering and relief of symptoms are due to the action of the drug directly upon nerve tissue or smooth muscle, there is evidence to support the view that the effects observed may be the resultant of a number of changes in hormonal equilibrium. The antithyroid effect of thiocyanate is well known. Clinically, patients suffering from hypertension may show a decrease in basal metabolic rate during thiocyanate therapy, rarely to myxedematous levels.[12, 18, 19] Thiocyanate may induce goiter in man [19] and rats.[20] Potassium thiocyanate markedly inhibits the uptake of radioiodine by the thyroids of rats.[21] Through the use of radioactive sulfur, thiocyanate has been found to penetrate not only the cells of the rat's thyroid but also those of the adrenal gland and liver.[22] Healy considered that the toxic manifestations of his hypertensive patients on large doses of thiocyanate resembled Addison's disease; one patient even developed pigmentation of the buccal mucosa and flexor surfaces of the elbows while taking the drug.[23] The diuresis from thiocyanate described in rabbits and man,[10, 23, 12] the increased phenolsulfonphthalein excretion observed in the present study, and the reported trends toward improved renal function of hypertensive patients during thiocyanate therapy, as measured by the clearance of urea, uric acid,[13] diodrast and inulin,[24] all suggest an improvement in tubular function associated with alterations in activity of the adrenal cortex and pituitary gland. Davis, Tanturi and Tarkington [25] and also Davis, Tarkington and Anderson [26] recently reported that during the administration of large doses of thiocyanate the lipid granules nearly disappear from the zona glomerulosa of the adrenal cortex of man and of dogs. They consider that these histologic findings substantiate the hypothesis that thiocyanate depresses adrenal cortical activity.

While the present study is not extensive enough to permit final conclusions as to the mode of action or the therapeutic efficacy of thiocyanate, the trend toward lower blood pressure levels and relief of symptoms is clear. The patients not only feel better but also experience a positive sense of well being. These effects come on gradually as the blood level of thiocyanate

rises, and become most pronounced shortly after an effective blood level has been attained. The subsequent relationship of drug therapy to the clinical course is variable: in certain patients, improvement continues throughout the period of therapy, while in others there is a tendency to escape from the thiocyanate effect after a time, and in still others a remission in the hypertensive state persists after withdrawal of the drug. These characteristics are consistent with the view that the effect of thiocyanate may be a humoral one, mediated by one or more of the glands of internal secretion.

That the lowering of blood pressure and symptomatic improvement are more closely related to thiocyanate therapy than to the doctor-patient relationship was indicated in the following ways:

1. There was a definite correlation between blood thiocyanate level and a sense of well being. This feeling was the most pronounced when the patient had been taking thiocyanate for from one to three months, shortly *after* a peak thiocyanate level (12 to 18 mg. per cent) had been reached, and was often preceded by several weeks of weakness and lassitude. The blood levels were unknown to patient and physician at the time the symptoms were recorded and blood pressures determined. If the improvement were due to mental suggestion alone, one might expect the greatest effect prior to this period.
2. Patients showed a rise in blood pressure and/or a recrudescence in symptoms after thiocyanate was replaced by a placebo.
3. In the period following thiocyanate therapy, some patients showed a gradual return of blood pressure to its former high level, while in others lower pressures persisted over a period of months. While this observation has been used as an argument against specificity of effect,[27] it equally well suggests that thiocyanate may produce a remission in the disease, as do iodine or thiouracil in some cases of hyperthyroidism.

To illustrate, a 58 year old colored woman who had had a hemiplegia five years previously complained of many distressing symptoms, including weakness, shortness of breath, dizziness and headaches, and of feeling nervous, muddled and shaky. She was completely relieved of all her symptoms by a three month course of thiocyanate, and her blood pressure fell moderately. She moved to West Virginia when her blood level was high—15.6 mg. per cent; the drug was stopped when she left Baltimore. She wrote that she remained completely free from symptoms for several months when, following a hard cold, they started up again as severely as ever.

Since many features of the natural history of hypertension are still obscure, such as the lack of close correlation between symptoms and blood pressure levels, the nature and extent of factors producing exacerbations or remissions, and, indeed, the basic uncertainty as to whether "essential hyper-

tension" comprises one disease or many, it is hard to "prove" the beneficial effect of treatment on this protean disease. As with other therapeutic measures designed to modify the course of essential hypertension, such as sympathectomy, rice diet or low sodium diet, the objective study of the clinical response to thiocyanate has been overshadowed by controversy between the "good effect" and the "no effect" contenders. Whereas the beneficial effects described by early workers have been substantiated by many clinical observers,[28, 29, 30, 31] others have found the average changes in blood pressure for the treated group to be of doubtful statistical significance.[27] Moreover, repeated warnings have appeared in the literature as to the dangerous nature of the drug, the seriousness of toxic effects with the possibility of untoward death.[15, 22, 33] Without entering the controversy over toxicity, I should like to remark that thiocyanate is not alone among useful drugs in its toxic potentialities, and to emphasize that guidance by accurately determined thiocyanate blood levels is essential. When this is done, serious toxic effects have rarely been encountered by those who have had wide experience in using the drug.[12, 34, 14, 23, 28, 29, 30]

In any event, as a result of the unfavorable reports thiocyanate has been somewhat categorically discarded, as is indicated by the following quotations from current textbooks of medicine:[35, 18]

"Tissue extracts, vegetable extracts, vaccines, hormones, nitrites, sedatives, pyrogens, phlebotomies, thiocyanates, and sympatholytic agents have all been administered for hypertensive disease, only to be abandoned."

"Thiocyanate must be regarded as a special sedative, to be used with caution or not at all, rather than as a specific."

Implicit in most of the work on thiocyanate therapy is the concept that there is a single cause of hypertension which should be reversed or cured by a single drug. Both experimental and clinical observations, however, have led many of us to believe the opposite hypothesis, namely, that the elevation of blood pressure in hypertension is the resultant of multiple etiologic factors, and that there is a constant interaction of various neurogenic and humoral pressor mechanisms.[36-49] The probability that thiocyanate regulates but one of these factors, and that when one pressor mechanism is depressed another may take its place, has been largely overlooked. This concept is supported by the observations of Davis and Barker, who found that patients whose high levels of blood pressure were not controlled by thiocyanate therapy alone became susceptible to thiocyanate control following sympathectomy, although, in this refractory group, sympathectomy alone also was usually unsuccessful.[14] In conclusion, therefore, it seems rational to regard thiocyanate as an effective therapeutic tool to be used alone or in combination with other measures directed toward reducing pressor activity, as the needs of the individual patient indicate.

Summary

1. Thiocyanate is a pharmacologic substance which has been found to depress blood pressure levels and relieve symptoms in essential hypertension for a period of many months.

2. These effects were observed in a majority of 19 hypertensive patients studied for several years both on and off the drug, and were found to be most prominent shortly after effective blood levels of thiocyanate were attained. The later effects of thiocyanate both on blood pressure and on symptoms were more variable.

3. Recent experimental studies concerning the effect of the thiocyanate ion upon endocrine activity, particularly of the thyroid and adrenal glands, are reviewed.

4. The hypothesis that the mode of action of thiocyanate in hypertension is through an indirect humoral mechanism is discussed.

5. While thiocyanate may not control all of the mechanisms responsible for hypertensive disease, its clinical effectiveness and the recent experimental evidence of its action on endocrine glands justify its continued therapeutic trial and further investigation into its mode of action.

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TREATMENT OF CENTRAL NERVOUS SYSTEM CRYPTOCOCCOSIS: A REVIEW AND REPORT OF FOUR CASES TREATED WITH ACTIDIONE *

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INTRODUCTION

IN a previous review,[9] the morbidity and mortality of cryptococcosis were discussed. It was shown that infection with the cryptococcus was usually fatal. Of approximately 220 published cases of the disease, 33 cases were alive at the time of their respective reports. Nineteen of these did not have central nervous system disease and, of this group, 13 appeared to have been completely cured; these included bone, scalp, skin, lung and nasopharyngeal lesions. On the other hand, of the 14 cases who were still alive with central nervous system disease, only one could be considered cured. This was the case of Marshall and Teed,[47] in which sulfadiazine was the therapeutic agent employed. A six year follow-up of this case (personal communication) leaves no doubt as to the clinical and laboratory criteria of cure, since both the cerebrospinal fluid findings and neurologic examination were completely normal. In the remainder of the patients there were persistent cerebrospinal fluid findings (either pleocytosis or positive cultures) or inadequate follow-up data for proper evaluation; also, several of these patients have since died.

These findings would seem to demonstrate the high mortality of the central nervous system disease; 86 per cent of these cases die within the first year, the majority (70 per cent) within the first three months after onset of symptoms. (See figure 1.) It should be noted, however, that there are a small number of cases with a seemingly indolent central nervous system infection who had survived up to nine years after onset,[55] still with positive cerebrospinal fluid cultures and clinical evidence of meningeal involvement. Willard and Wolff [77] have likewise noted a tendency toward remission during the clinical course of the disease. These facts must be borne in mind in evaluating attempts at therapy of the central nervous system form of the disease.

REVIEW OF THERAPEUTIC AGENTS PREVIOUSLY EMPLOYED

In the reported cases of central nervous system cryptococcosis, a wide variety of agents has been employed, all without appreciable success except

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for the use of sulfadiazine in Marshall and Teed's case,[47] as previously noted; sulfadiazine was of no use in all other cases in which it was used. On the other hand, several of these agents have been of distinct value in the treatment of those cases without central nervous system involvement, with the iodides, sulfadiazine and protoanemonin [12] being credited with cures of lung [13] and other lesions. Table 1 lists the various drugs and agents which

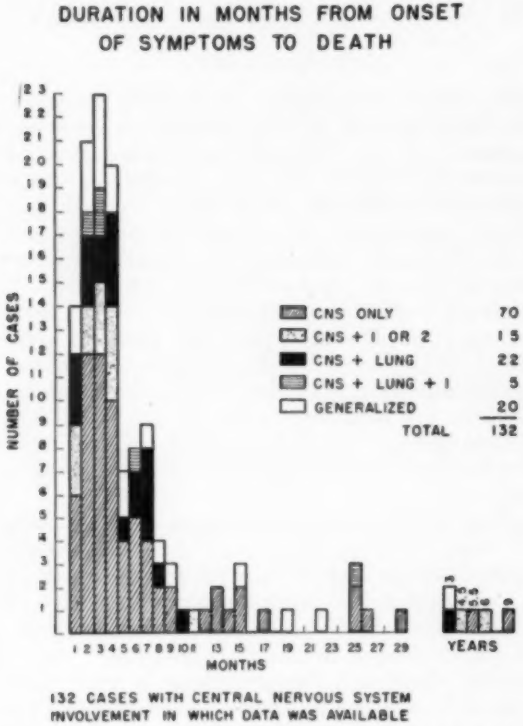


FIG. 1. Duration in months from onset of symptoms to death in cases of central nervous system cryptococcosis.

have been used in attempts at therapy of the central nervous system form of the disease.

AGENTS FURTHER CONSIDERED

Of this large and heterogeneous group the following agents deserve more detailed consideration, as far as the central nervous system disease is concerned:

Vaccine Therapy: The immunologic information concerning *Cryptococcus neoformans* is sparse, most strains having poor immunogenic capacity.[50]

Benham [5] divided pathogenic and nonpathogenic strains of the genus Cryptococcus into four groups on the basis of serologic and morphologic characteristics. Evans [18] has recently divided Benham's Group III (isolated from human infections) into three serologic groups, using immunized rabbits.

TABLE I

Agents Used in Therapy of Central Nervous System Cryptococcosis *

Antibiotics
- Actidione—†, 3, 10, 17, 19, 26, 28, 31, 32, 44, 66
- Penicillin—19, 27‖, 49
- Protoanemonin—†
- Streptomycin—50, 57, 72
- Terramycin—†
- Tyrocidin—28
- Aureomycin—‡
- Chloromycetin—‡

Physical Agents
- Fever therapy
  - Cabinet—†, 49
  - I.V. typhoid vaccine—49
- Radiotherapy—14, 65, 75

Heavy Metals
- Arsenicals
  - Oxophenarsine HCl—48
  - Tryparsamide—14
- Antimony compounds—20, 48
- Colloidal silver—61
- Colloidal copper—65
- Gold sodium thiosulfate—65

Immunologic
- Autogenous vaccine—6, 52, 54, †
- Immune rabbit serum—61

Other Agents
- Acriflavine—31
- Alcohol, intravenous—48
- Alkalinization—49
- Atabrine—24
- Furacin—49
- Gentian violet—36, 60
- Hexamethylenamine—65
- Iodides—14, 19, 28, 61, 68, 71
- Mercurochrome—7
- Methylene blue—9a
- Promin—
- Quinine—61
- Sulfonamides—11, 19, 25, 27, 36, 47, 53, 55§, 67, 71
  - Sulfadiazine
  - Sulfanilamide
  - Sulfapyridine
  - Sulfaseptasine
  - Sulfathiazole
- Thymol—36
- Tricresol—61
- Vitamin D—24

* Partial list of references.
† Author's cases.
‡ Not tried in human; no use in animals.
§ Thought to have influenced favorably course of disease, but not a cure.
‖ Reduction of number of organisms in cerebrospinal fluid, but not a cure.

A mild form of hypersensitivity, usually revealed by skin reactions, has been found to occur in many patients with cryptococcosis.[24] Dienst,[16] for instance, injected intracutaneously into a human case of cryptococcosis 0.1 c.c. of a sterile solution of killed organisms diluted in saline to a constant turbidity of one billion organisms per cubic centimeter. Within 24 hours, this produced an erythematous area 2 cm. in diameter which lasted 24 hours. He also found that rabbits could be sensitized in a like manner. Urbach and Zach [69] found that there was a high-grade specific skin allergy to intracutaneous injection of blastomycin (made from *C. neoformans*). Bernhardt [6] likewise used a similar antigen with positive skin reactions and felt

that his case (a skin infection) had improved with repeated intracutaneous injections.

In one of our cases (A. M.),[58] skin testing was performed for sensitivity to *C. neoformans.* Antigens were prepared as follows: (1) Capsulated cryptococci: A suspension of the patient's organisms was taken from agar into saline, diluted to 1 per cent and heated in a bath at 100° C. for 10 minutes. (2) Noncapsulated cryptococci: The above 1 per cent suspension was treated with HCl for one and one-quarter hours at room temperature, washed twice with saline, resuspended and heated as above for 10 minutes. Positive reactions were obtained with both types of antigens, as evidenced by appropriate wheals.*

This and other positive evidence for antibody production has led to the use of vaccines in the therapy of the central nervous system form of the disease. Shapiro and Neal[61] used an intravenous vaccine in a case of cryptococcic meningitis, with no effect. O'Neill et al.[62] reported a case of meningitis treated with a vaccine, with cure of the patient. Details are lacking concerning preparation of the vaccine, as well as adequate follow-up data of cerebrospinal fluid chemistries, cells and cultures, making the case impossible to evaluate; sulfonamides were also used.

One might thus conclude that attempts at vaccine therapy of both the systemic and central nervous system form of the disease have been disappointing. Further study along immunochemical lines, such as that of Neill[60] with isolation of specific polysaccharides from the capsules of the cryptococci, should prove more fruitful in this respect.†

Fever: Kuhn[41] noted that mice were readily infected with strains of *C. neoformans* obtained from human cases of cryptococcic meningitis, and that death occurred following a regular increase in the number of viable organisms in the mouse tissues. This did not hold for the rabbit, the animals resisting infection and the number of viable organisms in the tissues decreasing regularly. He noted that the body temperatures of mice and rabbits differed, with a mean temperature of 99.1° F. for normal mice and a mean temperature of 103.5° F. for normal rabbits. The growth of cryptococci at varying temperatures was then studied, and it was found that at higher temperatures fewer organisms were produced and viable cells decreased in number; at 107° F., only 2.5 per cent of viable cells survived after 24 hours. It was felt that the resistance of the rabbit to infection might be a function of its higher body temperature.

These studies were further amplified,[42] and it was found that acclimated mice with elevated body temperatures lived longer than normal mice when both were infected with a pathogenic strain of *C. neoformans.* Kuhn[42]

* Antigens were prepared by Dr. Margaret Holden, of the Department of Bacteriology, College of Physicians and Surgeons, Columbia University.

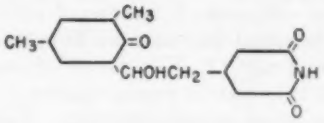
† Dr. James Trimble, Department of Dermatology, College of Physicians and Surgeons, Columbia University, has been investigating the polysaccharides in the capsules of the organism.

suggested that elevated body temperatures might be a useful adjuvant in therapy of human cryptococcosis.

Seegal [58] likewise had earlier noted the inhibiting effect of elevated temperatures on the growth of the organisms, and also found [20] that the action of actidione was potentiated by elevated temperatures in vitro, in keeping with the observations of Kuhn.

Kligman et al.[38] studied the effect of temperature on the survival of chick embryos infected intravenously with *C. neoformans*. They found that the survival rate of the embryos varied directly with progressive temperature elevation, as shown by experiments in which embryos had been infected and incubated originally at 37° C. (to insure infection), and then subsequently incubated at temperatures varying between 39° and 42° C. They noted that the organisms were completely destroyed in the chick embryos incubated at 42° C. for a period of eight days.

ACTIDIONE



PROTOANEMONIN

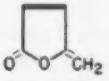


FIG. 2. Chemical structure of actidione and protoanemonin.

Possible collateral evidence concerning the effect of elevated body temperature on human infection was obtained from a case of central nervous system cryptococcosis (P. V.), who developed a severe epididymitis of nonfungous origin, with a fever of 105° F. for several hours. Following this episode he showed considerable clinical improvement in his central nervous system status. Kligman [39] likewise mentions a case of cryptococcic meningitis with coexisting malaria who improved following the paroxysms of fever. He, too, on the basis of this and the laboratory work above described, suggested the use of fever therapy in human central nervous system infection. Fever therapy (cabinet) was also used in the case reported below (case 1, R. H.), with no readily assessable effect from a total of 48 hours at 103°F.

There is thus a fairly good basis for the use of fever in the treatment of cryptococcosis, particularly as an adjuvant form of therapy.

Protoanemonin: Protoanemonin is a lactone (see figure 2) which can be prepared synthetically [2, 62] but which was obtained from a member of the plant Ranunculacae, namely, *Anemone pulsatilla* (buttercup). This compound was found to exhibit antibiotic activity [25, 59] against the cryptococcus, this being due to the double bonds in the molecule, since saturation of these bonds destroyed the activity. The lactone structure itself appeared to have no significant antibiotic effect, but served only to maintain the double bond at the end of the chain. Attempts at alteration of the chemical configuration of the drug did not materially increase its antibiotic activity or decrease its toxicity.[2]

Protoanemonin has been used in five cases of cryptococcosis, four with central nervous system involvement and one with a cryptococcic lesion of bone.* The drug appeared to cure the bone lesion, the patient dying subsequently of an unrelated cause; this case has been reported elsewhere.[12] The first of these cases with central nervous system involvement (A. M.) [9a] was one with a cryptococcic granuloma of the cauda equina, who received two intrathecal injections of protoanemonin, 1 mg. each diluted in 10 c.c. saline. The drug was discontinued because of failure to obtain positive cultures from the cerebrospinal fluid obtained at operation. No toxic signs were noted. The second case (P. V.), one of cryptococcic meningitis, received three intrathecal injections of protoanemonin, 1, 2 and 3 mg., respectively diluted in 15 c.c. saline, at daily intervals. There was no immediate reaction to injection, but on the fourth day following start of therapy the patient was unable to void, and had diminution of reflexes in the lower extremities and partial saddle anesthesia. It was felt that he had a cauda equina syndrome with a neurogenic bladder, this latter being verified on cystometric study. Subsequently his bladder function recovered and the saddle anesthesia disappeared. He improved somewhat following a nonspecific epididymitis (see section on fever therapy) and was discharged. Follow-up revealed a sudden demise, still with a low-grade meningeal infection. The third case (case 1, R. H., reported in detail below), with an indolent cryptococcic meningitis, received protoanemonin, 4 to 10 mg. in 10 c.c. saline intrathecally twice a week for a period of two months to a total dosage of 100 mg. (See figure 3.) Cultures were generally positive during this period. There were no immediate toxic manifestations, except burning upon administration of the drug. The final case (L. C.) also had cryptococcic meningitis, receiving intrathecal protoanemonin twice a week in doses of 5 to 6 mg. in 10 c.c. saline. In addition, he received intravenous protoanemonin, 350 mg. in 250 c.c. saline. Six days before death he inadvertently was given approximately 10 times the previous intrathecal doses (60 mg.), with much burning in both legs and severe headache, but no vasomotor

*The data on protoanemonin were kindly furnished by Dr. Margaret Holden and Dr. Beatrice C. Seegal, of the Department of Bacteriology, College of Physicians and Surgeons, Columbia University, in whose laboratory the basic work on the drug was performed. The studies reported here were carried out under their supervision.

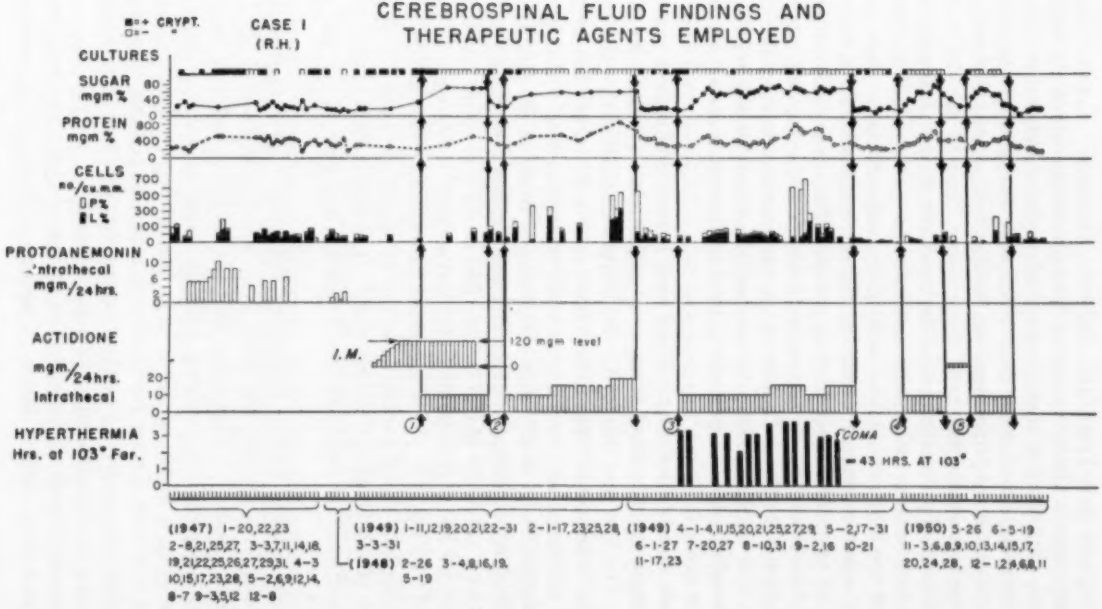


FIG. 3. Case 1 (R. H.) Cerebrospinal fluid findings and dosage of actidione and protoanemonin.

changes. Two days later he had developed urinary retention and bubbling râles throughout both lungs, and died soon thereafter. Lumbar puncture immediately prior to death revealed a thick plastic exudate in the subarachnoid space, with only a small amount of material obtainable. Autopsy showed changes in the lumbar cord which were attributed to the excessive local administration of protoanemonin; he also had a widespread and severe cryptococcic leptomeningitis.

The efficacy of protoanemonin in the treatment of central nervous system cryptococcosis may be summarized as follows: Although temporary improvement was observed in two cases while under therapy, there was no change in sugar content or culture of the cerebrospinal fluid which could be taken as evidence of specific drug action. The drug exhibited definite toxicity, manifested by two neurogenic bladders and symptoms suggesting root irritation (R. H.). Despite its in vitro activity against the cryptococcus, it is of minimal efficacy in vivo and should not be used systemically or intrathecally because of its toxicity; local application, however, has proved of value as above indicated.

Bacillus subtilis Derivatives: There have been several reports concerning an antifungal agent isolated from an organism closely related to *Bacillus subtilis*. The first was that of Lewis, Hopper and Schultz,[45] who demonstrated that a substance from culture filtrates of a *B. subtilis*-like organism exhibited antifungal activity against certain pathogenic fungi. Landy, Warren, Rosenman and Colio [43] likewise isolated a strain of *B. subtilis* which possessed negligible antibacterial activity and striking fungistatic properties. The antibiotic substance obtained from this strain was called bacillomycin. This substance had a growth-inhibiting action on *C. neoformans* in concentrations of 0.05 mg./c.c. This compound had not been tried in human cases of cryptococcosis, except for one injection in one of our cases (S. B.), and the effects of this could not be evaluated. It is said to have a local irritant effect, manifested by sterile abscess formation and pain at the site of injection.[80] *

Recently Hobby, Regna, Dougherty and Stieg [33] have further studied the compound, designated Antibiotic XG, which was isolated by Lewis, Hopper and Schultz.[45] They found that the antibiotic had both fungistatic and fungicidal properties, varying with the experimental conditions used. It was found to be highly hemolytic in its present degree of purity, but they suggested that with further purification it might be possible to administer the material parenterally. For the moment they felt that it might have a place in the local chemotherapy of fungous diseases.

Walton and Woodruff [74] reported an antifungal agent, mycosubtilin, likewise isolated from subtilin broth. Complete inhibition of *C. neoformans*

* Bacillomycin B was kindly supplied by Dr. Joseph Seifter, of the Wyeth Institute of Applied Biochemistry, Philadelphia, Pa.

cultures was achieved with concentrations of mycosubtilin of 5 micrograms/c.c.

These antibiotic agents have not yet, to the author's knowledge, been tried against human central nervous system infections with *C. neoformans*, but from the preliminary laboratory work they would seem to warrant clinical trial if more purified and less toxic products become available.

Miscellaneous: Animal experiments have been performed with other chemotherapeutic agents, but in general these agents have been too toxic, although exhibiting action against the cryptococcus. Robinson et al.[37] first showed that streptothrycin inhibited *C. neoformans*. This work was elaborated by Solotorovsky et al.,[24] who found that there was a prolonged survival rate in mice treated with streptothrycin. The drug is too toxic for human use. A similar state of affairs exists with atabrine,[8] in which *C. neoformans* was inhibited by concentrations of atabrine far above those levels achieved in the human without toxic manifestation.

Drouhet and Segretain [10] showed that hyaluronidase destroyed the capsules of the cryptococci in the concentrations used; this has not been the experience of this laboratory. It is interesting to speculate on the possible greater efficacy of various antifungal agents if dissolution of the capsule could be accomplished by hyaluronidase.

Fisher [19] tried propamidine, aureomycin, penicillin and sulfadiazine in infected mice, with negative results.

The most extensive laboratory work in the study of therapeutic agents active against the cryptococci has been reported recently by Kligman and Weidman.[29] Their studies may be summarized as follows:

Antibiotics: The following antibiotics were effective against the cryptococci: actidione, bacillomycin B, allein, pleurotin, protoanemonin, tomatin and eumycin, the first four being most effective. Ineffective were tyrothrycin, crude penicillin, penicillin G and K, streptomycin,[4] penicillic acid, tyrocidin, gramicidin, subtilin, bacitracin, gladiolic acid, glutinosin, crepin, kojic acid and aspergillic acid.

Fatty Acid Derivatives: Pelargonic, capric and undecylenic acids were effective in vitro, but their effect was antagonized by whole blood.

Miscellaneous: The naphthoquinones (particularly menadione) showed a strong in vitro activity, but blood inactivated the effect. On the other hand, the thiocarbamate derivatives maintained their activity in the presence of whole blood but had no effect in vivo. Sulfonamides [27] had no effect in a 1:4,000 dilution in vitro.

Actidione: * In 1945 Waksman, Schatz and Reilly,[38] working with *Streptomyces griseus*, reported a second antibiotic produced by that organism in addition to the already familiar streptomycin. Whereas streptomycin was insoluble in organic solvents, this second antibiotic could be extracted in

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small quantities from the culture filtrate of *Streptomyces griseus* and in larger quantities from the mycelia by the use of acetone or ether. Such an extract exhibited antibiotic activity against gram-positive but not against gram-negative bacteria.

In the following year, Whiffen, Bohanos and Emerson [76] likewise found an antibiotic in the beer of *Streptomyces griseus* cultures. They were the first to note that this substance, still in crude preparation, exhibited marked fungicidal properties, particularly for *C. neoformans*. They showed that *C. neoformans* was inhibited in a 1:1,000 dilution of a beer of *Streptomyces griseus* containing at the same time 130 micrograms of streptomycin per cubic centimeter, and also that the same organism was not inhibited by 285 micrograms per cubic centimeter of highly purified streptomycin. Further, they showed that *C. neoformans* was completely inhibited by this fungicidal antibiotic from *S. griseus* in dilutions up to 1:1,300,000.

Subsequent work by Ford and Leach [21] and by Ford, Leach and Whiffen [22] has shown that this substance, known as actidione, is a diketone with the formula illustrated in figure 2. Kornfeld and Jones [40] also elucidated

TABLE II

LD_{50} Dose of Actidione in Animal Species[70]

Species	Route	Dose
Mice	Intravenously	150 mg./kg.
Guinea pig	Subcutaneously	60 mg./kg.
Rabbit	Intravenously	17 mg./kg.
Cat	Intraperitoneally	4 mg./kg.
Rat	Subcutaneously	2.7 mg./kg.
Rat	Intravenously	2.5 mg./kg.

the chemical configuration of the antibiotic. They found that the substance was rapidly inactivated by dilute alkali at room temperatures.

Acute toxicity experiments in animals where the LD_{50} was calculated revealed a wide variation of the toxic dose in different animal species. This is illustrated in table 2, the data being obtained from Ford and Leach [21] and confirmed by Hellstrom and Seegal [30] for mice and rats. In addition, it has been shown [70] that percutaneous application of the drug is fatal to rats in a dosage of 0.5 c.c. of 5 per cent actidione in 45 per cent ethanol, the animals dying in from one to three days, all exhibiting severe diarrhea. It should be noted, however, that the drug could be injected into the cisterna magna of rabbits without apparent toxic effects.[58]

Two assays of actidione have been developed. The first is that of Loo et al.,[40] an application of the filter paper disc method used for streptomycin originally, but using *Saccharomyces pastorianus* ATCC 2366 as the test organism. The second assay is that developed by Hellstrom,[29] also a modified filter paper disc method but using *C. neoformans* as the test organism.

Using a standard tube dilution technic, Hellstrom [30] noted antifungal activity of actidione for a variety of fungi, and particularly for *C. neoformans*,

from different human cases of the disease; table 3 illustrates the findings in this regard. Fisher [19] likewise found actidione effective in vitro against the cryptococci but not in vivo in mice. Hellstrom also noted the presence of the drug in body fluids of man—serum and urine—following intramuscular injection.[20] However, with the dosage and assay method used, a clinically satisfactory blood level method was not evolved.

TABLE III

Minimal Inhibitory Concentrations* of Actidione, Protoanemonin and Bacillomycin B, for Various Strains of Fungi and Bacteria
Data from Hellstrom and Seegal[20]

Strains	Actidione	Protoanemonin	Actidione and Protoanemonin†	Bacillomycin B
Cryptococcus neoformans				
D. B. (Case 3)	6.0	[40.0		
S. B. (Case 2)	0.2			
P. C. (12)	0.04	2.0		
‡L. C.		8.4		
R. H. (Case 1)	0.37	2.0	0.2	10.0
H. O.	0.07			
A. M. (9a)				
Montefiore	0.2	10.0		
‡P. V.		10.0		
Wa.	0.27			
B. K. (Case 5)	0.50			
Nonpathogenic cryptococci	0.2	4.0		
S. cerevisciae	0.16	6.0	0.16	
S. pastorianus	1.0			
Fusarium (D. Bo.-Case 6)	4.0	10.0		40.0
C. immitis	100.0	2.0		
E. coli	1,000.0	10.0	8.0	
Staph. Oxford	100.0	7.0	20.0	

* All values in micrograms/c.c.
† Combination of actidione and protoanemonin found to be extremely toxic in animals; not tried in humans.
‡ See text under protoanemonin.

CLINICAL EXPERIENCES WITH ACTIDIONE

The clinical use of actidione in cryptococcosis of the central nervous system may be discussed under two headings, as follows:

Review of Previously Treated Cases: The author is aware of 10 cases of cryptococcosis of the central nervous system treated with actidione at other clinics.

Echols and Garcia [17] treated a case of cryptococcic meningoencephalitis in coma with a total of 1,400 mg. of actidione. The dosage schedule consisted of 580 mg. intramuscularly in eight days, the highest dose being 120 mg. in 24 hours; 810 mg. intravenously in 16 days, the highest dose being 180 mg. in 24 hours; and 4.5 mg. intrathecally. Spinal fluid cultures had been consistently positive before therapy. Before death, 10 consecutive cerebrospinal fluid cultures were negative, the first negative culture appearing after a total of 450 mg. of the drug had been given in five days. A rapid

drop in temperature and clinical improvement were noted when the drug was given; it was felt that the patient's life had been definitely prolonged. At autopsy, in addition to a leptomeningitis, there were lesions in the basal ganglia and brain stem from which organisms were recovered. The authors were somewhat encouraged by the response to the drug.

Haspel [28] reported a case of generalized cryptococcosis with positive blood and cerebrospinal fluid cultures. The organism was completely inhibited by a concentration of actidione of 1:100,000. Actidione was started in a dose of 20 mg. and was doubled two days later, the patient receiving 40 mg. daily thereafter for 18 days. Clinically, the patient showed some improvement in appetite and mental state, but despite a drop in temperature her condition rapidly deteriorated and she died on the eighteenth day of therapy. Autopsy revealed diffuse involvement by *C. neoformans* of brain, spinal cord, pericardium, kidneys, adrenals and lungs.

Higgins [21] treated a young boy with a basilar arachnoiditis and secondary hydrocephalus due to cryptococcic leptomeningitis. Dosage was begun with 10 mg. intramuscularly twice a day and increased to 60 mg. twice a day five days later. Subsequently, dosage was reduced to 30 mg. twice a day. Spinal fluid cultures remained positive during therapy, but the number of organisms was reduced. It was felt that the temperature curve had shown some improvement during therapy, but the patient died soon thereafter.

Levy [44] treated a 58 year old female with a proved cryptococcic lesion of lung as well as a previously removed cryptococcic granuloma of the cerebellum, who subsequently developed cryptococcic meningitis. The patient was given actidione intramuscularly in doses of 30 mg. per day. The drug was also given intrathecally, in doses of 10 mg. per day, and intraventricularly, in doses of 20 to 30 mg. per day. Within 24 hours of initiating therapy with actidione, cerebrospinal fluid cultures were negative and remained so thereafter. The patient showed concomitant clinical improvement, but died suddenly of what proved to be an unrelated pulmonary infarct. Autopsy revealed no cryptococci in the cerebrospinal fluid or meninges, yet immediately beneath the surface of the meninges were viable organisms. It was felt that the actidione had acted in the cerebrospinal fluid as an in vitro experiment and had not penetrated the barrier of the meninges or affected the organisms in the brain itself. Nor had the intramuscular injections had an effect on the organisms in brain or cerebrospinal fluid.

Cawley [10] apparently treated a case, but data are unavailable at this time.

Hill [20] reports the case of a 21 year old white female with cryptococcic meningitis. Actidione was started intramuscularly, in doses of 10 mg. every eight hours, being increased to 10 mg. every six hours; the total dosage was 330 mg. in 10 days. Two weeks after start of therapy, cerebrospinal fluid cultures were negative; data concerning cells, sugar, etc., were not available. The patient was discharged improved; follow-up was likewise not available.

Sweigert and Mayer [60] used actidione on a female patient with cryptococcic meningitis. The dosage was 30 mg. per day to a total of 600 mg. She improved symptomatically but developed a subcutaneous nodule under therapy. Her cerebrospinal fluid still showed a pleocytosis of 30 to 40 cells. Her course was downward, but further data are unavailable.

August [1] mentions a female patient with cryptococcic meningitis in whom a remission occurred while under treatment with actidione, 10 mg. per day (route uncertain) for one month, and sulfadiazine; cerebrospinal fluid data were not given. The only toxic effect was nausea and vomiting.

Fisher [19] treated a seven year old boy with cryptococcic meningitis whose organisms (cultured from the cerebrospinal fluid) were sensitive to actidione in vitro. Actidione was given intramuscularly, in doses of 20 mg. per day for nine days, with no evidence of improvement or toxicity. The drug was also given intraventricularly in doses of 1 mg., 5 mg. and 10 mg. on successive days. There was a drop in the cerebrospinal cryptococci count from 66 to 10 per cu. mm., and two days later to zero. The cerebrospinal fluid cultures also showed a striking drop in the number of organisms. The patient showed no clinical improvement and therapy was stopped; the patient ultimately died in decerebrate rigidity. The author felt that the drug probably had some fungicidal effect in vitro, provided it could be brought into direct contact with the organisms.

Greenwald [26] mentions a case of a 30 year old white male with arachnoiditis of the posterior fossa due to cryptococcic leptomeningitis diagnosed at operation. Actidione was used in therapy with no improvement; dosage schedule was not available.

Summary

Actidione has been used in doses ranging from 10 mg. twice a day to 30 mg. four times a day by the intramuscular route. It has been given intravenously in doses as high as 180 mg. per day. It was used intrathecally in doses of 4.5 and 10 mg. per day. Finally, it has been given intraventricularly in doses of 20 to 30 mg. per day. The only visible toxic effects were nausea and vomiting; no change was noted in the hematologic status of the patients on whom data were reported. Clinically, the drug appeared to affect favorably the temperature curve in several patients, this being concomitant with some slight clinical improvement. Despite the drug, most of the patients died, with one remission reported. Two observers noted sterilization of the cerebrospinal fluid during therapy, which was thought by one [44] to be the equivalent of an in vitro effect.

Case Reports

The following reports concern four cases of cryptococcic meningitis, one case of Fusarium meningitis, and one case of noncentral nervous system cryptococcosis, all treated with actidione:

Case 1 (R. H.) This patient was first seen in the Chest Clinic of Presbyterian Hospital at the age of 47 years, with the chief complaint of chronic cough of three years' duration, productive of less than 1 ounce of sputum per day. A few râles were heard at her left lung base, and x-ray of the chest revealed bilateral infiltration radiating out from both hila. For this reason she was admitted to the Medical Service for work-up.

First Presbyterian Hospital Admission (January 9 to January 28, 1945): Physical examination was negative except for an apical systolic murmur. Laboratory data were also negative, except for the previously mentioned x-ray findings; erythrocyte sedimentation rate, 18 mm./hr.; total protein, 6.8 gm. per cent (albumin, 4.8; globulin, 2.0); four sputa examinations negative for acid-fast bacilli, one sputum negative for fungi by culture, and tuberculin skin test negative in 1:1,000 dilution. Pulmonary function tests were also within normal range. It was felt that tuberculosis, fungous disease, progressive pulmonary fibrosis and lymphoma were ruled out, and that Boeck's sarcoid was the most likely diagnosis in view of the negative tuberculin test and suggestive punched-out lesions of the phalanges on x-ray. The patient was discharged with this diagnosis, to be followed in the Chest Clinic.

Second Presbyterian Hospital Admission (March 12 to March 17, 1945): Patient was re-admitted to the Medical Service because of paroxysmal attacks of severe fronto-occipital headache associated with nausea and vomiting. These headaches had been present for many years, occurring every six to eight weeks and lasting five to six hours, and were unrelieved by medication. The possibility of a pheochromocytoma was considered because of previously noted fluctuations in blood pressure with occasional hypertension observed in Clinic. However, during her hospital stay her blood pressure remained consistently normal, and cold pressor tests were negative. She was again discharged to Chest Clinic.

During the remainder of 1945 the patient continued to complain of frequent headaches and chilly sensations. She was seen often in Psychiatry Clinic, where it was felt that her complaints were functional in origin. In January, 1946, she underwent a dilatation and curettage because of vaginal bleeding, with no evidence of neoplasm revealed. In November, 1946, she complained of many and varying pains in chest, back and arms, together with a daily fever of 101 to 102° F. In December, 1946, she was seen in Neurology Distributing Clinic with the above complaints, plus severe headache and diplopia, and was referred to Group Clinic for further study. Again laboratory studies were negative, including blood counts, urine, Kline, erythrocyte sedimentation rate, agglutinations, blood cultures and chest x-ray (showing some clearing of previous hilar markings). Because of the headache, which was now more severe and frequent, the diplopia and the unexplained fever, she was admitted to the Neurological Institute for work-up.

First Neurological Institute Admission (January 17 to May 16, 1947): The pertinent findings on physical and neurologic examinations were as follows: A middle-aged, right-handed German housewife in moderate distress. Her musculature was flabby but not atrophied. There were bony deformities at the distal interphalangeal joints suggestive of osteoarthritis. She exhibited slight ataxia of gait, more marked in the right leg, with some difficulty in walking on heels and on a straight line. The equilibratory and nonequilibratory tests were poorly done, with clumsiness in performing succession movements and skilled acts with hands and fingers. There was generalized hyporeflexia, with a questionable right Babinski. The disc margins were blurred bilaterally, the left more so than the right. The pupils reacted to light and accommodation, with no diplopia elicited. Hearing was diminished bilaterally, with bone conduction better than air conduction and the Weber test lateralized to the left.

Laboratory findings revealed the following: blood counts normal; visual fields normal; reduction of both air and bone conduction to high tones on audiometric test-

ing; calorics normal; electroencephalogram showed no clear-cut focal signs but was interpreted as a mildly irregular record; myocardial damage and a right bundle-branch block on electrocardiogram; tuberculin test negative in 1:10,000 dilution. Skull x-rays revealed atrophy of the dorsum sellae and posterior clinoid processes suggestive of increased intracranial pressure; review of all the chest x-rays since February 20, 1947, showed an unchanging picture of symmetrical and diffuse increase in density of the parenchymal shadows throughout both lung fields, somewhat more marked in the lower halves; degenerative arthritic changes at the interphalangeal joints were seen in x-rays of the hands; bronchoscopy was negative; lumbar puncture revealed a spinal fluid protein of 258 mg. per cent; sugar 26 mg. per cent; and a positive culture for *Cryptococcus neoformans*. (See figure 3 for detailed laboratory data.)

With the diagnosis of cryptococcic meningitis thus established, attempts at therapy were begun with intrathecal injections of protoanemonin, the patient receiving doses of 4 to 10 mg. (in 10 c.c. saline) twice a week for a period of two months, to a total dosage of approximately 100 mg. During this period, cerebrospinal fluid cultures were consistently positive (21 of 25 samples from as many lumbar punctures). In addition to the protoanemonin she received a course of fever therapy, with a total of seven hours at a temperature of 105.8° (not shown in figure 3), this being terminated prematurely because of the development of permanent electrocardiographic changes directly attributable to the hyperthermia. During her stay she continued to run a low-grade fever, and her symptoms continued unabated. She was discharged to the Neurology Clinic and followed at intervals with lumbar punctures and cerebrospinal fluid examinations.

Second Neurological Institute Admission (September 2 to September 13, 1947): Patient was re-admitted three and one-half months later because of daily vertex and suboccipital headaches and continuous generalized bone-pain, having had these complaints since discharge. In addition, she had noted earache and bilateral hearing loss of two weeks' duration. Neurologic examination was unchanged from her previous admission.

Repeated cerebrospinal fluid cultures again revealed cryptococci, and she was accordingly given a course of streptomycin, receiving 3 gm. per day intramuscularly for seven days, and 0.1 gm. intrathecally (in 4 c.c. of saline) on two occasions. There was no appreciable change in the cerebrospinal fluid findings during this interval, except for a moderate protein increase, the cultures remaining positive and sugar depressed. Streptomycin was discontinued because of the development of tinnitus, nausea, vomiting and nystagmus. She was discharged again to Neurology Clinic.

Third Neurological Institute Admission (February 25 to March 21, 1948): Patient was re-admitted five months later (having done well in the interim), complaining of low-grade fever and generalized aches and pains of several weeks' duration.

On examination the patient showed an uncertain, unsteady gait, slight anisocoria, somewhat sluggish pupillary reactions, slight awkwardness of succession movements of extremities, moderate impairment of air conduction on the left, and low-grade fever.

Lumbar punctures revealed slightly elevated cerebrospinal fluid pressures, increased total protein (288 to 396 mg. per cent), reduced sugar content and pleocytosis. *Cryptococcus neoformans* was cultured from the first cerebrospinal fluid specimen (February 26, 1948), but not from subsequent punctures.

Patient received four intrathecal injections of 1:2,200 protoanemonin in amounts of 1.5, 2.5, 5 and 5 c.c., respectively (0.75 to 2.5 mg.). There was moderate but definite improvement in subjective complaints, with marked diminution in her severe, deep "bone" pain in the extremities, disappearance of burning sensations in her face and a feeling of well-being. However, there was no appreciable change in her

neurologic status, and she was discharged again to Clinic to receive twice weekly protoanemonin injections.

Fourth Neurological Institute Admission (October 28 to December 8, 1948): Patient was re-admitted again because of difficulty in walking, manifested by dizziness, staggering gait and frequent falling. At times after falling she was unable to get up by herself because of extreme weakness and dizziness. In addition, incontinence of urine had appeared in the two weeks prior to admission.

On physical examination she appeared chronically ill and walked with short, mincing steps, obviously apprehensive about falling. Equilibratory and nonequilibratory tests were poorly performed on the left side, and she exhibited a generalized areflexia with a positive left Oppenheim. There was a fine nystagmus, particularly on right lateral gaze. Hearing tests revealed a slight diminution of hearing on the right side.

Her cerebrospinal fluid cultures remained positive, and she was given three intrathecal injections of protoanemonin without change in status. She was again discharged to Clinic.

Fifth Neurological Institute Admission (January 10 to July 2, 1949): Patient was re-admitted one month later and remained in the hospital for a period of six months, during which time she received three courses of actidione therapy, as outlined in figure 3. During each course of therapy her cultures became negative, and the low cerebrospinal fluid sugars returned to normal levels. She was discharged again to Clinic.

Sixth Neurological Institute Admission (September 15 to September 20, 1949): Patient was re-admitted at this time because of a fall, with resulting severe lower back and leg pain. However, work-up revealed no evidence of fracture, and her spinal fluid was negative for *C. neoformans*. Accordingly, she was discharged without further therapy.

Seventh Neurological Institute Admission (November 11 to December 16, 1949): Patient again fell and was re-admitted for re-investigation. Examination was unchanged except for tenderness over T-11 vertebra. X-rays of lumbosacral spine revealed compression fractures of the bodies of T-12 and L-2. Cerebrospinal fluid findings are as shown in figure 3. She was given a Taylor brace and gradually mobilized, and was discharged home much relieved of pain. It was felt that further therapy with actidione should await marked exacerbation of symptoms.

Eighth Neurological Institute Admission (May 25 to July 9, 1950): Because of increasing headache, poor memory and inability to walk unassisted, patient was re-admitted for further therapy with actidione (fourth course). This consisted of a course of nine intrathecal injections, together with intramuscular dosage as noted in figure 3. There was noted again the rise in cerebrospinal fluid sugar and the persistent negative cerebrospinal fluid cultures with concomitant clearing of mental status. Therapy was discontinued because of increasing evidence of radicular irritation, manifested by severe pain following intrathecal injection of actidione. The patient was again discharged to be followed in Clinic.

Ninth Neurological Institute Admission (November 1 to December 19, 1950): Patient was re-admitted six months later, having failed rapidly in the few weeks before admission. She was mentally obtunded and could not carry out simple commands. Examination revealed generalized cog-wheel rigidity and fixed facies, with a periodic tremor noted in all extremities. There was no papilledema, and the remainder of the neurologic examination was unchanged. She was started on her fifth course of intrathecal actidione, in dosage of 10 mg. O.D. She showed some initial improvement in mental status, which was mainly attributed to rehydration and restoration of electrolyte balance. Her course was static for the remainder of her admission. The changes in her cerebrospinal fluid findings are discussed below. She

was discharged to Montefiore Hospital for chronic nursing care. Follow-up reveals no change in status at this time.

An evaluation of the results of actidione therapy in this case is given below:

(a) *Cultures:* As shown in the accompanying tables, the cerebrospinal fluid cultures became negative on the fourth, sixth, fourth, second and first days after the start of intrathecal actidione therapy in each of five courses. They remained negative during the first and second course while therapy was continued; in the third course, positive cultures were obtained on the fourteenth, twenty-seventh, twenty-eighth and thirtieth days of treatment, with the remaining cultures negative. In the fourth and fifth courses all cultures remained negative after treatment was started. During the two previous years of cerebrospinal fluid study the cultures had been predominantly positive, with an occasional negative specimen. It was therefore felt that the drug had exhibited a definite inhibitory effect on the growth of the organism in the cerebrospinal fluid.

That this effect was transient is evident from the fact that the cultures were again positive on the seventh day after cessation of intrathecal therapy in the first and second courses (no specimens taken before the seventh day), and on the thirtieth day after cessation of therapy in the third course (one negative specimen before the fluid was positive). A positive culture was obtained between the fourth and fifth course (only one lumbar puncture). There was no appreciable effect (except in one instance, in which growth took 14 days) on the period of growth, most cultures when positive growing out in from two to six days.

(b) *Sugar:* * The sugars appeared to indicate even more evidence of drug action. They began to rise on the twelfth day of intramuscular therapy before intrathecal therapy was started, indicating that intramuscular therapy might have an effect on the disease process in the meninges. In the remainder of the courses a rise was noted on the third, fifth, second and second days, respectively, after the start of the intrathecal therapy, reaching normal on the fourteenth, seventh, fifth and fourth days, respectively, of therapy; in the first course of intrathecal therapy the sugars reached normal on the seventh day of therapy, but there had already been a rise following intramuscular therapy. Following cessation of therapy in all courses, the sugars were back at their low levels in 14, 12, 21, five and six days, respectively; it should be noted that lumbar punctures were not done every day following cessation of therapy, so that the actual fall in sugar (or return of positive cultures) might have occurred at an earlier time interval.

(c) *Protein:* During all courses of intrathecal therapy, as might be expected, there was a rise in the cerebrospinal fluid protein. This rise was impressive, reaching levels of 504, 860, 770, 600 and 450 mg. per cent,

* Actidione is not a reducing agent, as shown by negative results when set up against Benedict's solution and in the routine Folin-Wu test for sugar.

respectively, during each of the courses. Following cessation of therapy there was a return to the pretreatment levels of approximately 200 mg. per cent, which had existed before the use of intrathecal protoanemonin. It was felt that this rise was a manifestation of the irritant action of the drug on the meninges and spinal cord.

(d) *Cells:* During the first course of intrathecal therapy there was no appreciable change in the total number of white blood cells or in the relative percentage of lymphocytes and polymorphonuclear elements. However, during the latter portion of both the second and third intrathecal courses, there was a definite pleocytosis (as high as 500 in the first and 656 in the second, with an increase in polymorphonuclear cells). This was felt to be due to the use of 20 mg. actidione per dose during the second course and to a temporary increase to 15 mg. per intrathecal dose during the third course; a reduction of dose in the latter case resulted in a fall of the white blood cells. No pleocytosis was seen in the fourth course and only a moderate rise in the fifth course.

(e) *Pressure:* There appeared to be no relationship between the intrathecal use of actidione and the cerebrospinal fluid pressure.

(f) *Color:* During therapy there was an occasional specimen in which the fluid appeared to be yellower than usual, as well as several in which the fluid was definitely xanthochromic. The presence of red blood cells in the fluid could be definitely correlated with this xanthochromia and, in turn, with the aforementioned relatively larger doses of actidione (e.g., 15 and 20 mg.); with the reduction or cessation of dosage the xanthochromia (and red blood cells) disappeared. There is no doubt that in doses of 15 to 20 mg. the drug causes diapedesis of red blood cells into the cerebrospinal fluid to a varied extent.

(g) *Other Laboratory Data:* Careful weekly check was kept of hemoglobin, red blood cells, white blood cells, erythrocyte sedimentation rate, non-protein nitrogen, cephalin flocculation and electrocardiogram, with no change noted at any time during actidione therapy.

(h) *Clinical Toxicity:* Clinical toxicity manifested itself in two ways:

(1) *Vomiting:* Nausea and vomiting, particularly during the first course of intramuscular and intrathecal therapy, were an annoying complication. Control was finally achieved during all courses by using Dramamine, 100 mg. four times a day, where pyridoxine and phenobarbital had been of no avail. The vomiting usually appeared 30 minutes or so following either intramuscular or intrathecal medication and lasted for about 30 minutes. It was felt, therefore, to be of central origin.

(2) *Pain:* During therapy the patient occasionally experienced severe shooting and burning pains in both legs and buttocks, sometimes immediately following injections but more often apparently unrelated to the injections (intrathecal). It is of interest in this regard that the reflexes in the lower extremities could not be obtained after cessation of intrathecal therapy (three

courses), where they had been present (1 plus) before therapy was started. It was felt that the patient showed evidence of a mild radiculitis, probably secondary to intrathecal irritation of the nerve roots (although whether injections of protoanemonin had played a part could not be determined).

(i) *Clinical Improvement.* It was the feeling of all observers that the patient was much improved after her first three courses of actidione. Subjectively her headaches had disappeared; she was less dizzy; she could walk without aid, and her incontinence had cleared completely. Again, because of the previous clinical remissions, it was difficult to determine how much of her improvement could be attributed to the actidione. Her improvement was much less striking after the fourth course and was nil after the fifth course of therapy.

Case 2 (S. B.).* This 57 year old male was first admitted to the Presbyterian Hospital in May, 1946, with the chief complaint of painless swelling in the right parotid region.

First Presbyterian Hospital Admission (May 20 to May 22, 1946): Past history was negative except for fusion of his right knee many years previously, exact cause unknown. Physical examination was negative except for a diffuse, soft, painless swelling of the right parotid gland and moderate generalized lymphadenopathy, particularly of the right cervical region. With the suspicion of lymphoma entertained, a biopsy of two lymph nodes in the right posterior cervical triangle was performed on May 21. Examination of these specimens on quick section revealed that the normal architecture of the nodes had been almost completely replaced by densely packed small round cells with rounded or oval nuclei. Mitoses were frequent. There was very little fibrous tissue, and no typical Dorothy Reed cells were seen. It was felt that this was compatible with a diagnosis of lymphosarcoma of the lymphocytic cell type. Accordingly, radiotherapy was instituted, with several courses to neck, cheek, axilla, abdomen and chest, with regression of previously enlarged nodes.

Second Presbyterian Hospital Admission (June 12 to June 13, 1949): Patient was re-admitted in June, 1949, because of signs of pleurisy with effusion. A thoracentesis was performed, with removal of 1,300 c.c. of bloody fluid and complete relief of symptoms.

Third Presbyterian Hospital Admission (September 7 to September 17, 1949): Three months later patient was re-admitted because of intermittent attacks of severe, watery diarrhea unassociated with nausea, vomiting or fever. Physical examination revealed generalized lymphadenopathy, with a 3 by 2 cm. right supraclavicular node and a 3 by 2 cm. left inguinal node. The spleen could be palpated 3 cm. below the costal margin, and the liver edge 2 cm. below the costal margin.

Laboratory work-up demonstrated the absence of any specific enteric pathogens. Liver function tests were normal. The gastrointestinal series revealed a retroperitoneal tumor which displaced the stomach, as well as evidence of abnormal intestinal motility compatible with either mesenteric lymphosarcoma infiltration or nutritional deficiency.

The patient received a course of nitrogen mustard therapy and was discharged improved.

First Neurological Institute Admission (October 11 to October 17, 1949—Died): Patient was admitted 25 days later to the Neurological Institute, with the chief complaints of double vision and headaches of three to four weeks' duration. On Septem-

*This case is reported through the courtesy of Dr. Carmine T. Vicale, Neurological Institute, New York.

ber 17, 1949, he had first noted double vision upon arising, with the false image occurring above the true one. This double vision had been transient, recurring at intervals up to the time of admission, particularly when the patient looked to the left. One week prior to present admission, he noted occipital headaches which were dull, aching in character, and only partially relieved by aspirin. In addition, with the onset of headache he had experienced intermittent periods of hiccoughing lasting for 20 to 30 minutes at a time. These symptoms increased slowly in frequency and severity.

Physical examination revealed an emaciated white male, oriented but in severe pain. There was tenderness to pressure over the base of the cervical spine and in the suboccipital region. The right knee joint was ankylosed; there was generalized lymphadenopathy, and the liver edge was felt 3 cm. below the costal margin.

Neurologic examination revealed minimally impaired finger-to-nose tests and succession movement bilaterally. The myotatic reflexes were equal with the exception of slightly reduced left achilles and hamstring reflexes; no pathologic reflexes were elicited. There was paresis of the left external rectus muscles. The remainder of the neurologic examination was normal.

Laboratory data were as follows: hemoglobin, 11.5 gm.; red blood cells, 3.1 million; white blood cells, 3,240; polymorphonuclears, 28 per cent; lymphocytes, 70 per cent; eosinophils, 2 per cent; erythrocyte sedimentation rate, 71 mm./hr.; non-protein nitrogen, 31 mg. per cent; CO_2 combining power, 60 vol. per cent; serum bilirubin, 0.3 mg. per cent; routine urine, normal; urine culture, *Streptococcus viridans;* sputum and spinal fluid, negative for acid-fast bacilli on culture; cerebrospinal fluid findings indicated in table 4. X-rays of the skull were negative.

Lumbar puncture revealed yeast-like organisms on smear which were thought by the technician to be cryptococci. Subsequent cultural studies verified this diagnosis. Actidione therapy was started on the fourth hospital day as follows: 1 mg. dose intramuscularly to test for sensitivity or idiosyncrasy, this being increased to 2 mg., 5 mg. and 10 mg. at four-hour intervals; then 10 mg. every four hours for 24 hours; then 15 mg. every four hours; then 40 mg. every four hours. Intrathecal therapy was likewise started with a test dose of 1 mg., then raised to 10 mg. O.D.; then 10 mg. twice daily; then 20 mg. twice daily. Intravenous medication was given in doses of 100 mg. O.D. in slow drip (in 500 c.c. saline). The patient showed no toxic reactions that could be attributed to the drug, but neither was there any change in his clinical course, which was steadily downward. Toward the end of his hospital course the cerebrospinal fluid became almost gelatinous in consistency, and pink-tinged on one occasion, but subsequent taps did not show this phenomenon. He exhibited periods of rationality, but soon became comatose and died on the sixth hospital day.

Autopsy. At autopsy a widespread cryptococcic leptomeningitis was found, with minimal inflammatory changes present. Moderate numbers of cryptococci were found throughout the leptomeninges. Honey-combed lesions were found in the basal ganglia, internal capsule, thalami and dentate nuclei of the cerebellum. These lesions again showed only minimal inflammatory changes, although the organisms could be clearly seen. There were no changes in the lumbar, thoracic or cervical cord indicative of toxic action of the intrathecal actidione; organisms and a few clusters of lymphocytes in the leptomeningeal nerve sheaths were the only pathologic findings.

In addition, the patient showed a lymphocytic lymphosarcoma with widespread involvement of epicardium, liver, lungs, spleen, pancreas, kidney, adrenals, lymph nodes and bone marrow. Small foci of cryptococci were detected microscopically in lung, kidney and spleen.

Case 3 (D. B.). This 21 year old female, with the diagnosis of Hodgkin's disease of the mediastinal and peripheral lymph nodes, was found to have an osteolytic lesion in the left hip, acetabulum and superior ramus of pubis which was progressive

in nature. Biopsy of the acetabulum revealed *C. neoformans* of a pathogenic type. It was felt, in view of her profound respiratory embarrassment and her lack of response to all other therapy (including repeated radiotherapy, etc.) aimed at her mediastinal and hip lesions, that a trial on actidione was warranted. Her organism was sensitive to actidione in a dilution of 1:200,000. Dosage was started at 5 mg. every six hours for the first day and gradually increased to 50 mg. every six hours by the fourth day of therapy. A total dosage of 1,000 mg. was given in approximately eight days. Her course continued steadily downward, with hyperthermia, tachycardia and continued respiratory distress. She was relatively unresponsive during the 24 hours immediately prior to death.

There was no perceptible effect of the actidione on either the hip or mediastinal lesions. The only evidence of toxicity was nausea and vomiting following the first injection (30 minutes); this was subsequently controlled by sodium luminal (30 mg.) one hour prior to each injection. No local pain was experienced.

Case 4 (J. A.).* This 44 year old white male was admitted to the Neurological Institute of New York on January 9, 1951, with the following complaints: easy fatigability; anorexia; 15 pound weight loss in eight months; drenching night sweats of five months' duration; severe, paroxysmal, occipital headaches associated with dizziness but no vertigo of four and one-half months' duration; episodes of confusion of one month's duration; nausea, vomiting and staggering gait of three weeks' duration.

Physical and neurologic examinations were as follows: pulse, 64; blood pressure, 160/90 mm. of Hg; respirations, 20. Well oriented but complained bitterly of occipital headache. Gait unsteady, with staggering to either side; frequently required assistance. Strength and tone normal. Cerebellar functions within normal limits, except for some terminal tremor on finger-to-nose and hand-to-knee tests. Reflexes hyperactive but equal throughout, with bilateral Babinski's and positive right Chaddock's signs. Cranial nerves were normal, with no papilledema. During attack of headache, patient had horizontal nystagmus in either direction of lateral gaze.

Laboratory data revealed the following: hemoglobin, 14.2 gm.; red blood cells, 4.72 million; white blood cells 8,500; polymorphonuclears, 85 per cent; lymphocytes, 12 per cent; monocytes, 1 per cent; eosinophils, 2 per cent; erythrocyte sedimentation rate, 10 mm./hr.; Mazzini, negative. Skull x-rays were normal. Chest x-ray showed a suspicious increase of density in left third interspace anteriorly. Lumbar puncture (done before admission) revealed IP, 260 mm. cerebrospinal fluid; protein, 54 mg. per cent; sugar, 52 mg. per cent; chlorides 640 mg. per cent; white blood cells, 4 (polymorphonuclears, 1; lymphocytes, 3). Culture was not done.

Impression. It was felt that the symptoms and signs were all compatible with a posterior fossa, midline, obstructing lesion, either an ependymoma of the fourth ventricle or a cystic hemangioblastoma.

Operation. On January 12, 1951, a ventriculogram was performed. This revealed symmetrical dilatation of both lateral ventricles, a slight amount of air in the third ventricle, a nonvisualized aqueduct, and a small amount of air in the fourth ventricle. The cervical cord was also outlined and was strongly suggestive of herniation of the cerebellar tonsils. It was felt that these findings indicated a posterior fossa tumor, probably in the cerebellum. Accordingly a suboccipital craniectomy was performed. There was moderate increase of pressure in the posterior fossa, with herniation of both cerebellar tonsils through the foramen magnum. Exploration of the fourth ventricle, needling of both cerebellar hemispheres, was negative for tumor. The cerebellar tissue was extremely friable, and a large intracerebellar hemorrhage occurred during retraction on the left cerebellar hemisphere. This was removed,

*This case is reported through the courtesy of Dr. Hyman Weitzen and Dr. Lester A. Mount, Neurological Institute, New York.

along with a portion of the cerebellum; fresh tissue examination showed normal cerebellar folia, and the remainder was sent as specimen. Following this the wound was closed in the usual fashion, it being felt that an anterior, high-vermis lesion was still probably present and was not seen on exploration.

Course. Postoperatively the patient did fairly well for the first week, his course being characterized by moderate fever, persistent hiccoughing and slight restlessness; he was alert and responded well, moving all extremities. On the eighth postoperative day he became disoriented, extremely agitated and exhibited a rise in temperature. Review of laboratory data indicated that the ventricular fluid at the time of operation had 3 white blood cells and many "yeast contaminants"; total protein was 47 mg. per cent. Accordingly, repeat lumbar puncture on January 20 and 22, the eighth and tenth postoperative days, revealed white blood cells, 134; polymorphonuclears, 85 per cent; lymphocytes, 14 per cent, with many yeast forms (7,200/cu. mm.); cerebrospinal fluid sugar was 27 mg. per cent. The yeast forms were identified as *Cryptococcus neoformans* on smear, culture and animal inoculation. Blood cultures, throat smears, gastric washings and urine specimens were all negative on direct smear for cryptococci.

TABLE IV

Case 2 (S. B.)—Cerebrospinal Fluid Findings and Actidione Dosage

	10-12-49	10-13-49	10-14-49	10-15-49*	10-16-49	10-17-49**
CSF: Culture (Crypt.)		+	+	+++		
CSF: Sugar mg./100 c.c.	45	58	44	50		56
CSF: Protein mg./100 c.c.	78		52	53		
CSF: Cells—Total (per cu. mm.)			45	24		
CSF: % Polys.			0	0		
CSF: % Lymphs.			100	100		
CSF: Organisms (per cu. mm.)	+		1,200	2,200		900
CSF: Pressure (mm. CSF)	440	480	420	140		
Blood Culture				+		
Actidione—I.M.		2	47	60	120	80
(mg.)—Intrathecal		1	20	30		
			(10–10)	(10–20)		
Bacillomycin B (mg.)—I.M.						50

* Fluid pink gelatinous.
** Death.

With the diagnosis of cryptococcic meningitis established from the findings in the cerebrospinal fluid (and verified by positive pathologic examination from cerebellar tissue taken at operation), the patient was started on vigorous actidione therapy. He received intramuscular, intrathecal and intraventricular actidione, the latter via indwelling ventricular catheter; the dosage is indicated in table 5. There was no clinical response to this form of therapy (the patient had previously been on terramycin empirically because of fever), and his condition rapidly deteriorated. The patient died on the fourteenth postoperative day, five days after start of actidione therapy. It was felt that there was no visible evidence of toxicity due to actidione, the intraventricular medication being well tolerated. The organisms in the spinal fluid continued to multiply in the face of tremendous doses of actidione, and it was apparent that this was an overwhelming infection.

TABLE V

Case 4 (J. A.)—Cerebrospinal Fluid Findings and Actidione Dosage

		1-6-51	1-11-51	1-12-51	1-20-51	1-21-51	1-22-51	1-23-51	1-24-51	1-25-51	1-26-51	Total
CSF	Culture (Crypt.)	—	—	—			+	+	+	+		
	Sugar mg./100 c.c.	52			46		27	119*	176*	326*		
	Protein mg./100 c.c.	54	80	47								
	Cells—Total (per cu. mm.)	4	13	3	134			1,300	100	180		
	% Polys.	25	0		86			100	100	100		
	% Lymphs.	75	100		14			0	0	0		
	Organisms (per cu. mm.)			"yeasts"	"yeasts"		7,200	6,000	4,800	5,000		
Actidione (mg.)	I.M.					41	480	600	720	600	600	2,681
	Intrathecal					20	10	10	10	10	10	70
	Intraventricular						5	5	5	5	5	25
												2,776

* Patient receiving large amounts of 50 per cent dextrose intravenously.

TABLE

Case 5 (B. K.)—Cerebrospinal

1951		2-9	2-19	2-23	3-7	3-7	3-13	3-15	3-16	3-17	3-18	3-19	3-20
CSF	Culture (Crypt.)		+	−	+*	+	−	−	−				−
	Sugar mg./100 c.c.		46	45	47			62	66			66	68
	Protein mg./100 c.c.	155	172	154	42			98	89		80	78	74
	Cells—Total	191	180	350	140	260		100				60	348
	(per cu. mm.) % Polys.	52		10	6	8							6
	% Lymphs.	48	100	90	94	92		100				100	94
	Pressure (mm. CSF)							100	120	140	140	120	100
Actidione—Intramuscular (mg.)—Intrathecal									120	120	120	120	120
									10	10	10	10	10

* Ventricular fluid.

Autopsy. Autopsy revealed a widespread meningoencephalitis due to *Cryptococcus neoformans.* The basilar exudate had caused a mild hydrocephalus. In addition, there was infection of the ventricular surfaces, as well as an acute, generalized, yet mild ventricular ependymitis. The lungs, kidneys, thyroid and adrenal glands were involved by the organism. There was no evidence of histologic damage that could be attributed to actidione.

Case 5 (B. K.).* This 59 year old white female was admitted to the Neurological Institute of New York on February 5, 1951, with complaints of headache, depression, fatigue and inability to work of five weeks' duration. The headache was made worse by sudden change in position. She had experienced several febrile episodes in the past few months, with temperatures to 100° F.

On admission her neurologic examination was normal, but her course in the hospital was progressive, with development of the following findings: marked ataxia of gait with persistent tendency to fall backwards; rotary nystagmus in both directions of gaze, right greater than left; early papilledema in right fundus; slight nuchal rigidity and suboccipital tenderness; bilateral intention tremor, and poorly performed finger-to-nose test bilaterally.

Laboratory data revealed: hemoglobin, 12.8 gm.; red blood cells, 4.02 million; erythrocyte sedimentation rate, 30 mm./hr.; blood sugar, 105 mg. per cent; urine, normal; Mazzini, normal. Lumbar puncture revealed total white blood cells, 191; polymorphonuclears, 52 per cent; total protein, 155 mg. per cent; sugar, 46 mg. per cent; chlorides, 604 mg. per cent. Spinal fluid cultures were negative on several occasions for fungi and bacteria, including tubercle bacilli. Skull x-rays were negative, with the pineal gland calcified and in normal position. Gastrointestinal series and chest x-rays were normal. Electroencephalogram was diffusely abnormal without focal signs. Visual fields were normal. Audiometrics and caloric studies were normal.

In view of the high protein, pleocytosis and low sugar in the cerebrospinal fluid, a higher organism infection such as tuberculosis or cryptococcosis was considered. Repeated cultures for the latter were negative. Because of the progression of the neurologic signs, particularly the accentuation of the previously blurred disc margins, it was felt that a ventriculogram should be done to rule out an expanding lesion. A

* This case is reported through the courtesy of Dr. Werner Hochstetter and Dr. Lester A. Mount, Neurological Institute, New York.

VI

Fluid Findings and Actidione Dosage

3–21	3–22	3–23	3–24	3–25	3–26	3–27	3–28	3–29	3–30	3–31	4–2	4–3	4–4	4–5	4–6	4–7	4–11	4–18	6–18
—	—	—	—		—	—	—	—	—	—	—	—	—		—	—	—	—	—
60	67	58			63	55	67	64	64		62	60	65	65	78	65	67	59	63
87	102	80			110	100	100	85	61		67	79	100	62	68	62	87	71	41
99	100	183			130	56	53	4	80		88		61	33	72	71	2	27	1
2									8		2		3						
98	100	100			100	100	100		92		98		97	100	100	100	100	100	100
100	90				120	110	160	140			120	130	120		90	125	125	100	140
120	120	120	120	120	120	120	120	120	120	120	120	120	120	120	2,400				
10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	200				
														Total	2,600 mg.				

combined ventriculogram and pneumoencephalogram, done on March 7, 1951, showed a normal ventricular system and subarachnoid spaces. Culture of the centrifuged ventricular and spinal fluid for fungus revealed cryptococci which were pathogenic for mice. Subsequent ventricular and spinal fluid cultures were also positive for cryptococci. The remainder of the laboratory data is shown in table 6.

With the diagnosis of cryptococcosis established, and with no other systemic evidence of the disease, the patient was started on intramuscular and intrathecal actidione therapy after the usual test dose by both routes (1 mg. intramuscularly and 1 mg. intrathecally). Dosage was raised to 10 mg. intrathecally O.D. and 20 mg. intramuscularly every six hours. The organism was shown to be inhibited in vitro by 0.5 microgram of actidione. Vomiting was controlled by Dramamine administration. This regimen was continued for 21 days, with a gradual rise in cerebrospinal fluid sugar to a level of 78 mg. per cent (cf. normal blood sugar), persistently negative cultures, and a gradual drop in protein and cells. There was a concomitant marked improvement in neurologic status, with disappearance of nystagmus, tremendous improvement in gait, and complete relief of headache. Patient was discharged on April 19, 1951, to be followed at frequent intervals.

Comment: This is the second case of a low-grade meningeal infection with cryptococci which has apparently been favorably influenced by a course of intrathecal actidione, as evidenced by improvement in cerebrospinal fluid findings. Follow-up two months after discharge revealed negative neurologic examination and normal cerebrospinal fluid (see table 6), indicating an apparent cure. Needless to say, the possibility of a spontaneous remission cannot be ruled out, but the cerebrospinal fluid changes are again suggestive of drug action. Fever therapy is being considered for this patient in conjunction with actidione intrathecally if symptoms and signs should recur.

Case 6 (D. Bo.) This two year old white male had been treated at another hospital for recurrent *Hemophilus influenzae* meningitis. Following admission to Babies Hospital, despite the use of serum, streptomycin and sulfadiazine, the patient continued to exhibit cerebrospinal fluid pleocytosis. Repeated cultures failed to reveal bacteria but grew out a saprophytic fungus, a Fusarium. A trial on actidione was

begun, since the organism was inhibited in vitro by 10 micrograms of actidione per cubic centimeter.

Dosage of actidione was as follows: 1 mg. intramuscularly every six hours for 24 hours; then 2 mg. every six hours for 24 hours; then up to 5 mg. every six hours, for a total daily intramuscular dose of 20 mg. This was continued for 15 days, with a total of 273 mg. actidione intramuscularly. Intrathecal medication was started with 1 mg. in 5 c.c. saline and increased 1 mg. per day until 10 mg. per day were being given, to a total dosage of 79 mg. actidione. (See table 7.)

TABLE VII

Case 6 (D. Bo.)—Cerebrospinal Fluid Findings in Case of Fusarium Meningitis, and Actidione Dosage

1951.....	5–9	5–28	5–29	5–30	5–31	6–1	6–2	6–3	6–4	6–5	6–6	6–7	6–8	6–9	6–10	6–11
CSF Culture*	±	+	−	+	+	−	+	+	+				+	−	−	
CSF Sugar mg./100 c.c.	41	43		26	38	44	48	40	34	33	38	35	45	45	45	40
CSF Protein mg./100 c.c.	53	91		85	86	94	93	87	115	96	90	82	88	92	90	86
CSF Cells—Total	630	1,800	1,500	5,760	2,000	1,900	2,840	1,530	2,100	2,000	770	1,180	1,800	1,450	2,200	
CSF % Polys.	50	75	66	90	90	85	90	90	90	65	85	90	90	90	90	
CSF % Lymphs.	50	25	34	10	10	15	10	10	10	35	15	10	10	10	10	
CSF per cu. mm.																
Actidione (mg.)																
I.M.		5	10	17	20	20	20	20	20	20	20	20	20	20	20	20
Intrathecal		1	2		2	2	4	5	6	7	8	9	10	10	10	

* Fusarium.

Prior to therapy there had been a marked fluctuation in the cerebrospinal fluid cell count and Fusarium cultures, the latter sometimes being negative. During the course of actidione therapy there was a progressive increase in the cerebrospinal fluid pleocytosis as well as in protein. The cultures remained positive at times and no change in growth potential was noted, e.g., length of time to grow out.

Clinically the child developed nuchal rigidity, positive Kernig's and Brudzinski's signs, and was moderately febrile and anorexic. The meningeal reaction continued throughout therapy, which was discontinued because of this and because of lack of influence on the disease process.

DISCUSSION

The interest in and incidence of cryptococcosis have been steadily increasing, especially in the past two years, as evidenced by the many publications dealing with various aspects of the disease. It is apparent that therapy achieves greater importance as more cases are reported, particularly with so high a fatality rate in the central nervous system form of the disease.

The difference in therapeutic results between the central nervous system and the noncentral nervous system cases is most striking, and to date no adequate explanation is forthcoming. This has been seen quite clearly in the case of protoanemonin, where the drug quickly cleared a local bone lesion and yet had no appreciable effect on the meningeal infections. Actidione, to the author's knowledge, has not been used against local lesions, but its in vitro effect as well as its sterilization of the cerebrospinal fluid in several of the patients above discussed should make it an excellent agent for

local therapy (e.g., skin, mucous membrane, and bone lesions accessible from the surface of the body, etc.).

The use of actidione in the central nervous system disease has been unsatisfactory, except for an occasional case; no infection has been cured, although some have been temporarily retarded. Although the drug has a very high inhibitory titer in vitro against the cryptococcus, in laboratory experiments with mice and other animals the majority of workers report no protection from the experimental infection.[19, 20] In humans actidione has been used in relatively small doses when the LD_{50} dose is compared to animals. Thus, the highest intravenous dose given in a 24 hour period was 180 mg. actidione,[17] which is 3 mg. and 2.5 mg./kg., respectively, for a 60 or 70 kg. person. This is equivalent to the LD_{50} dose for the rat but compares very unfavorably with that for the rabbit (17 mg./kg.) and mouse (150 mg./kg.). Perhaps the explanation of the failure of actidione to work in the central nervous system infections of man is the relatively low dosage employed; six times the abovementioned intravenous dose, or 1,080 mg., would be equivalent to the LD_{50} for the mouse. In one of our cases (case 4, J. A.), 2,681 mg. were given intramuscularly in one day but none was given intravenously.

Another criticism of the use of actidione is the lack of an easy assay method, preferably chemical, for following body fluid levels; the biologic assay methods above described do not seem adequate for the dosage used.

Future attack on the therapeutic problem would seem to be along two lines: (1) investigation of agents which would directly inhibit the growth of the organisms, or else destroy the polysaccharide capsules and thus make the organism more susceptible to direct action of other agents, such as actidione; (2) further exploration of the immunochemical approach, with investigation of the specific polysaccharides which compose the capsule or the organism, with the intent of using these serologic data in diagnosis and therapy.

Summary

1. A wide variety of drugs used in the treatment of central nervous system cryptococcosis have been reviewed. Almost universally they have been shown to be ineffective against the disease.

2. More detailed attention has been paid to the use of vaccine therapy, fever therapy, protoanemonin, *B. subtilis* derivatives and actidione.

3. Four cases of central nervous system cryptococcosis treated with actidione have been reported in detail. Two showed definite improvement in clinical and laboratory status during therapy and are still alive, one being an apparent cure; the others showed no response to the drug, both dying of a fulminating meningitis.

4. The toxicity of actidione is discussed at length. It is felt that the toxic manifestations do not prevent the use of the drug either by intra-

muscular, intravenous or intrathecal routes, provided reasonable vigilance is maintained.

5. From a review of all known treated cases, it is apparent that actidione is not very effective against central nervous system cryptococcosis. However, for want of other forms of therapy, and until other antifungal agents are available, it should be tried with caution and coupled with fever therapy, if possible. It may actually be indicated in the more indolent type of central nervous system infections.

6. The *B. subtilis* derivatives, particularly if they reach a stage of further purification, deserve further investigation in the treatment of the central nervous system form of the disease, although they may prove too toxic for use.

7. Study of specific antibiotic and chemotherapeutic agents should be continued. This, together with further research concerning immunochemical aspects of the organism, should yield data of therapeutic value.

Addendum

Since submission of this paper, Wilson and Duryea [78] have reported a case of cryptococcic meningitis apparently cured with actidione. Their patient, a 39 year old male, had complained of weight loss, vertigo, frequent headaches and nausea. Physical and neurologic examinations were normal. Cryptococci were isolated from the cerebrospinal fluid on direct examination and on culture. The cerebrospinal fluid sugar was reduced. In the six week period prior to institution of actidione therapy the patient became confused, irrational and incontinent, and developed ataxic gait and positive Babinski reflex.

The patient received three courses of actidione, with apparent sterilization of the cerebrospinal fluid following the first two courses of intrathecal and intravenous therapy. However, when actidione was discontinued, the cultures again became positive. Following the third course, again using both the intrathecal and intravenous routes, cultures remained persistently negative, and the patient has been asymptomatic and remarkably improved; data on sugar and cells at this time were not given.

Wilson and Duryea reported toxic symptoms from the use of 20 mg. actidione intrathecally per day, these consisting of marked signs of "cerebral irritation," presumably meningeal, as well as lethargy, mental depression, slurred speech and ataxia. Cessation of drug administration produced reversal of all these signs and symptoms. There appeared to be no evidence of toxicity by the intravenous route.

Recently a case of cryptococcic meningitis was treated at the Veterans Administration Hospital, Bronx, N. Y.* Here actidione caused an immediate remission of fever and some slight degree of clinical improvement,

* The patient was under the care of Dr. J. Sibley.

but subsequently the patient developed urinary suppression and died. Autopsy revealed a cryptococcic meningitis, organisms in the renal parenchyma and tubules, and widespread involvement of other organs. The question of renal toxicity of actidione could not be accurately evaluated, since evidence of renal insufficiency had been present on admission. This case is to be reported elsewhere in greater detail, with data on blood and cerebrospinal fluid actidione levels.

Finally, Marshall and Teed [79] have published a follow-up of their case [47] (discussed above under sulfadiazine) in which their patient was apparently cured.

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HEART DISEASE IN UNIVERSITY STUDENTS*

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ACCURATE knowledge of the incidence and cause of heart disease in the young adult population is of obvious importance. Unfortunately, there are many difficulties in the way of obtaining such information. The screening examinations carried out under the draft laws of World War II dealt only with males and did not result to the author's knowledge in any reliable statistics as to the incidence of the various types of heart disease.

Current knowledge of the incidence of rheumatic heart disease is obtained from diverse sources. There are available various surveys carried out in groups of school and pre-school children. There are a few long-term follow-up studies of these groups. There are mortality and morbidity statistics from the various departments of public health,[1] and various reports derived from surveys of postmortem examinations in large hospitals.[2, 14] Study of these sources not only reveals them to be inadequate where they are dealing with the young adult population, but also reveals marked variation in method, in reliability and in the results obtained. Such sources leave one without knowledge of the incidence of the various forms of heart disease in the young adult group.

It is surprising that more study has not been given to the incidence of the various forms of cardiovascular disease among college students. The student body of a large university or college, being composed of both males and females and readily controlled, lends itself well to such a survey. Such studies as have been reported vary greatly in apparent reliability, and are fewer and less complete than one would expect.

Any university student population is a selected one, and therefore any attempt to extrapolate the results of such a survey to the same age group of the general population in the same locality is likely to be misleading. In a large state-supported university such as the University of California at Berkeley, the modifying factors of selection must weigh less heavily than in smaller, more "private" institutions.

METHOD

I. *Student Processing.* The University of California at Berkeley has a student population of more than 20,000 individuals, almost all of the young adult age group. The average age of the entering student at this university is 20 years. Upon first entering the university, each student is processed through the Student Health Service situated in the Ernest V. Cowell Memorial Hospital. This is a hospital of some 150 beds, fully staffed and

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equipped as a general hospital and devoted entirely to the care of registered students. In this original processing of the entering student, he or she is first given a "Dispensary Record Card" upon which he must enter certain biographical and medical historical data such as place of birth, and history of injuries, deformities, diseases and operations.

In addition, there is printed on the card, to be checked if pertinent, a list of common diseases which includes such items as heart trouble, rheumatic fever, rheumatism, St. Vitus dance, scarlet fever, tonsillitis, discharging ear and nephritis. Having completed this part of his card, the student is then guided through x-ray, where a fluorogram of the chest is taken and read for lung and heart pathology, and through the various departments of dentistry, eye, ear, nose and throat, laboratory and medicine. In the course of this processing, the student receives a complete general physical examination, given by one or more practicing physicians. All abnormal findings are noted by the examiners on the Dispensary Record Card. These cards are then carefully reviewed and, where the history given by the student is suggestive or when abnormalities are noted by the examiners, the student is referred to the general clinic or to one of the specialty clinics for more complete diagnosis and treatment.

II. *Survey Groups.* For the purposes of the present statistical survey on the incidence of heart disease, two entering groups of students were studied. These comprised all students, male and female, entering the university for the first time and registering for the fall semester of 1949, and those entering college for the first time and registering for the fall semester of 1950. These groups comprised in all 11,096 students, of whom 7,566 were men and 3,530 were women. Immediately after their initial entrance processing, all students in these groups on whose Dispensary Record Cards appeared any history suggestive of heart disease, any notation of the presence of a heart murmur, or any physical findings suggestive of possible heart disease were referred to the cardiologist for evaluation. The author made every effort to see each of them at least once himself, and to arrive at a definitive diagnosis whenever possible. The total number of students thus referred and evaluated was 378, or 3.41 per cent of the entering students.

III. *Diagnostic Procedures.* In the individual cardiac evaluation of these 378 referred cases, careful inquiry was made as to the history of rheumatic fever in any of its manifestations, the birth history, the status of the individual's exercise tolerance, and the known duration of the murmur if one was present. A clinical evaluation of the cardiovascular system was made. Auscultation was performed in all cases before and after exercise, and in the erect, supine and left lateral positions. Cardiac fluoroscopy with x-ray films for measurement and electrocardiograms, which included standard and precordial leads, were taken in all cases in which there was any question of organic disease. Follow-up visits were frequently required. The criteria for diagnosis were strict and followed the Criteria for Diagnosis of Diseases

of the Heart of the American Heart Association.[3] All cases diagnosed as rheumatic heart disease were cases in which there was no doubt as to the diagnosis: identification of the various valvular lesions was based on clear clinical evidence. Again, diagnoses of congenital heart disease were made only when such diagnosis seemed well established. As a result of the application of such strict criteria, there remained certain cases in which the presence of heart disease and/or its etiology could not be established or definitely excluded. These cases were classified as "possible heart disease," and, together with the proved cases of heart disease, were listed for follow-up throughout their university careers. Heart murmurs found in the absence of organic heart disease were classified as "physiologic murmurs."

As will be discussed later, it became of interest to determine the numbers of individuals in each of these classified subgroups of rheumatic heart disease,

TABLE I

	Fall of 1949		Fall of 1950		Totals for 1949 and 1950		
	Men	Women	Men	Women	Men and Women	%	% Born in California
Total registering students	4,151	1,865	3,415	1,665	11,096	100.00	*50.9
Referred for cardiac study	131	61	128	58	378	3.41	
Chronic rheumatic ht. dis.	10	5	9	6	30	0.27	*23.3*
Mitral valve involved	5	3	6	6	20		
Aortic valve involved	6	2	5	1	14		
Mitral and aortic valve involved	1	1	2	1	5		
Congenital heart disease	4	2	2	4	12	0.11	58.3
Total proved heart disease	14	7	11	10	42	0.38	
Possible heart disease	13	4	7	2	26	0.23	50.0
Physiologic murmurs	104	48	106	33	291	2.62	55.3
Other (arrhythmias, etc.)	0	2	4	13	19		

* Based on a random sample obtained by taking every 40th registering student in the order in which they presented for processing at the Student Health Service.

congenital heart disease, possible heart disease and physiological murmurs who were born in the State of California. This information was readily obtained. To obtain the same data with reference to the entire survey group, a random sampling of the 11,096 entering students was made by consulting the Dispensary Record Card of every fortieth student taken in the same order in which they received their initial processing, and noting the percentage of the individuals in this random sample born in California. This random sample is believed to constitute an adequate and reliable control.

OBSERVATIONS

I. *Incidence of Heart Disease.* Perusal of table 1 will quickly reveal the findings in the two fall groups of entering students which were the subjects of survey. It will be noted that, of the 11,096 students surveyed, 0.27 per cent or 2.7/thousand, had proved rheumatic heart disease, and 0.11 per cent,

or 1.1/thousand, had proved congenital heart disease. The total incidence of proved heart disease was therefore 0.38 per cent, or 3.8/thousand. When it is noted that the incidence of "possible heart disease" constitutes an additional 0.23 per cent, or 2.3/thousand, it is apparent that the preceding incidence of proved heart disease constitutes a minimal figure. Physiologic murmurs deemed worthy of notation occurred in 2.62 per cent, or 26.2/thousand.

II. *Manifestations of Rheumatic and Congenital Heart Disease.* The relative incidence of the various rheumatic valvular lesions which were found among the group of entering students with proved rheumatic heart disease is also given in table 1. A more inclusive picture, however, is obtained by reference to table 2. Table 2 was derived by adding to the proved cases of

TABLE II

Classification of Rheumatic and Congenital Heart Lesions
Cases from table 1 plus other students being followed in fall semester 1950

	Men	Women	Total	% of Group
Chronic Rheumatic Heart Disease	41	16	57	100
Mitral insufficiency			39	68
Mitral stenosis			19	33
Aortic insufficiency			27	47
Aortic stenosis			5	8
Combined aortic and mitral			15	26
Congenital Heart Disease	15	9	24	
Pulmonary artery anomaly			7	
Interventricular septal defect			4	
Interventricular septal defect with Stokes-Adams syndrome			1	
Interauricular septal defect			2	
Patent ductus arteriosus			2	
Subaortic stenosis			2	
*Idiopathic hypertrophy			2	
Dextrocardia			1	
Congenital A-V block			1	
Unclassified			2	

* One proved by postmortem examination.

rheumatic and congenital heart disease disclosed by our fall surveys, all other students with proved heart disease of the same types who were attending the university during the fall semester of 1950. It should be noted that no duplication was involved in this addition. Due to the large turnover of students from semester to semester, the total number of each variety of heart disease which appears in table 2 bears no known relationship to the total university enrollment during that particular semester and therefore is not a measure of the incidence of heart disease in the total student population. It will be noted from table 2 that, in cases with rheumatic valvular involvement, mitral insufficiency was found in 68 per cent, aortic insufficiency in 47 per cent, mitral stenosis in 33 per cent, aortic stenosis in 8 per cent, and combined aortic and mitral valvulitis in 26 per cent. Thus, aortic insufficiency

ranked close behind mitral insufficiency as a clinical manifestation of chronic rheumatic heart disease and was more frequently found than clinical mitral stenosis. Among all proved cases of rheumatic heart disease a history of rheumatic fever was obtained in 63 per cent.

The various types of congenital heart disease may also be noted in table 2. Although several of these diagnoses rest on surgical or postmortem evidence, the majority are based on commonly accepted clinical concepts not supplemented by angiocardiography and other special diagnostic technics.

III. *Incidence of Heart Disease Among Native Californians.* It will be noted from table 1 that, of the total group of 11,096 entering students, some 51 per cent were born in California, as judged by a random sampling. Of the group with physiologic murmurs, 55 per cent were born in California. Of those with congenital heart disease, 58 per cent were born in California. These differences are not significant. Of those with rheumatic heart disease, however, only 23.3 per cent were born in California, and this difference is statistically significant. If we go further and find the incidence of rheumatic heart disease among the native-born entering students at California, we obtain an incidence of 0.124 per cent, or 1.24/thousand. This is not much greater than the figure of 1.1/thousand which was found to be the incidence of congenital heart disease.

Discussion

The first question that must be answered in any such statistical study as this is whether the method of screening was valid and reliable. In this survey, as in most others, the cardiologist saw only a small percentage (3.40) of the total number of individuals upon which the survey is based. That this can be a considerable source of error has been demonstrated strikingly by Wedum,[4] working with school children in Denver. Wedum found in one group of 1,945 girls, all examined by her, an incidence of rheumatic heart disease of 1.63 per cent, or 16.3/thousand. In another group of school children where the children were first screened by other physicians and then all suspects referred to her for diagnosis, the resulting incidence of rheumatic heart disease was only 0.48 per cent, or 4.8/thousand. Although these groups were not strictly comparable, Wedum concluded that the method of screening had a tremendous influence on the result obtained. In this survey it is undoubtedly true that some cases of heart disease were never referred for examination. It is our belief, however, that the referral of all those in whom murmurs were noted or on whose card any suspicious history appeared served to keep the number of missed cases to a minimum. It is probable that the true incidence of heart disease among the entering students may be higher than that here reported.

It is interesting to note how our incidence of heart disease compares with that found in other universities and colleges. Hedley [5] compiled data on the

incidence of rheumatic heart disease sent to him by the directors of health services of 86 colleges and universities in reply to his questionnaire. His compilations showed that, of a total of 104,163 student health examinations, 1,207 cases of rheumatic heart disease were diagnosed, an incidence of 11.6/thousand. The large probable error of this figure, however, is indicated by the varied methods and criteria applied by each responding institution, and is further illustrated by a refinement of the data given in Hedley's report. He found that if, of these 86 colleges and institutions, he considered only 14 which had close connection with a medical school and hence presumably better diagnostic facilities, then of 46,098 examinations there were 298 cases of rheumatic heart disease, an incidence of 6.4/thousand. Hedley accepted this figure as a much more reliable one. The available statistical studies from individual colleges or universities reveal great differences in method, reliability and result. Cole [6] reports at the University of Wisconsin an incidence of heart disease of 10.2/thousand, based on the review of accumulated student health records of 28,139 student examinations over an eight year period from 1931 to 1939. Wood [7] reports 31 cases of rheumatic heart disease among 3,086 students examined at the University of Pennsylvania during the years 1931–32, an incidence of about 10/thousand. A few lower incidence figures are quoted by Hedley: 4.6/thousand from Yale University [8] and 1.0/thousand from Minnesota. Our incidence of 2.7/thousand for rheumatic heart disease and 3.8/thousand total organic heart disease at the University of California at Berkeley is considerably lower than almost all other comparable reports.

When one considers congenital heart disease, it is apparent that little attention is given to it in most surveys. It is often not mentioned in the discussion of heart disease in university students, and one gains the impression that most congenital cases have been lost in the rheumatic group. Cole [6] reports the diagnosis of congenital heart disease in only eight of 28,139 students at Wisconsin, an incidence of less than 0.3/thousand and, in our opinion, much too low a figure. Other authors have simply applied the working hypothesis attributed to Wilson and Paul, that if heart defects are found in the physical examinations of school and other children, 80 per cent of these are rheumatic in origin. Such a hypothesis is not applicable to our data or to other data collected in California. Our incidence of 1.1/thousand of congenital heart disease appears quite in keeping with accepted disease rates.

It is our belief that the importance and prevalence of aortic insufficiency as a primary manifestation of rheumatic heart disease has been overshadowed by the stress placed in medical teaching upon the physical findings of mitral stenosis. Necropsy [9] findings have shown that involvement of the mitral valve occurs more frequently in rheumatic heart disease than involvement of the aortic valve. It is not surprising, then, that our findings showed more mitral insufficiency than aortic insufficiency. But it may be surprising to

some that aortic insufficiency was diagnosable almost twice as frequently as mitral stenosis. More striking still in this regard is the finding by the cardiovascular specialty board, as reported by Levy, Stroud and White,[10] that, among 271 cases of rheumatic heart disease in young Army rejectees studied in San Francisco, aortic insufficiency had the highest incidence of any valvular lesion! Among the other college reports Wood at the University of Pennsylvania finds that, of 31 cases of definite rheumatic heart disease, 23 had aortic insufficiency, an incidence of 74 per cent. That Cole, on the other hand, in his survey of cardiac disease at the University of Wisconsin, reports aortic insufficiency in only 15 per cent of cases of rheumatic heart disease is just another indication of the wide discrepancies among the various cardiac surveys. It is our belief that most reliable statistics tend to support a higher relative incidence of rheumatic aortic insufficiency than is commonly realized, and that more stress should be laid on the importance of careful auscultation for the aortic diastolic murmur and perhaps less on that so often misleading and misdiagnosed "mitral presystolic murmur in the left lateral position after exercise."

Of the various types of congenital heart disease encountered, little can be said. The great differences in relative incidence of these from each published series to the next are evidence of the difficulties of anatomic diagnosis in these cases without application of the recently developed specialized diagnostic methods and technics.

That the incidence of rheumatic heart disease is low in California has long been a prevailing impression and one supported by the vital statistics of the State [1] and by reports of surveys of school and pre-school children. But the question is still raised whether rheumatic fever is escaping diagnosis or not being reported. Our incidence figure of 1.24/thousand rheumatic heart disease among the native-born as compared with 2.7/thousand in the total student group entering the University of California is strong evidence for a low incidence of rheumatic fever in California. The method used obviated many errors intrinsic in those surveys which depend on the patient's history, his personal physician's diagnostic acumen, or the unraveling of the complications of travel and residence in various parts of the country.

As has been previously stated, it would be unwise to assume on this basis that the incidence of rheumatic heart disease generally in the young adult native-born population of California is 1.24/thousand and not much greater than the incidence of congenital heart disease. There are some indications, however, that this may be so. Robinson et al.,[11] in their study of heart disease among San Francisco school children in 1947, found 4.4/thousand with organic heart disease, comprising 2.43/thousand rheumatic and 1.9/thousand congenital. Sampson, Christie and Geiger [12] in 1947 found corresponding figures of 3.7/thousand, with 2.2/thousand rheumatic and 1.4/thousand congenital. If one applies the conclusion of T. Duckett Jones, that of a series of rheumatic children only some 40 per cent will have

clinical signs of rheumatic heart disease when they reach college age, our derived incidence of 1.24/thousand for native-born students at California is quite in keeping with these figures.

That striking variations in the incidence of rheumatic fever may exist in different localities within the State of California has been demonstrated by Sampson et al.[13] In their survey of the incidence of heart disease and rheumatic fever in school children in three climatically different California counties they found 20.7/thousand in one area and 4.6 and 1.5/thousand in the other two. Wedum, too, has pointed out the marked variations which can occur with both locality and time. We believe that the University of California draws so widely and generally upon the State for its student population that such local differences are of little significance in this report.

Summary

The incidence of heart disease among 11,096 entering students at the University of California at Berkeley was studied.

The total incidence of proved heart disease was 3.8/thousand, of which 2.7/thousand were rheumatic heart disease and 1.1/thousand congenital heart disease. There were, in addition, 2.3/thousand diagnosed as "possible heart disease."

The incidence of proved rheumatic heart disease was considerably lower among students born in California than in those born elsewhere. An incidence of rheumatic heart disease of only 1.24/thousand was found among those born within the State.

Aortic insufficiency is a relatively more frequent and important manifestation of rheumatic heart disease than is generally realized. The importance of careful auscultation for an aortic diastolic murmur should receive greater stress.

It is suggested that the incidence of clinically demonstrable rheumatic heart disease among native-born Californians of this age group is relatively little higher than the incidence of congenital heart disease.

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TREATMENT OF NONTUBERCULOUS BACTERIAL PLEURAL SPACE INFECTIONS WITH AUREOMYCIN: RESULTS OF TREATMENT IN NINE PATIENTS; CONCENTRATION OF AUREOMYCIN IN PLEURAL AND PERICARDIAL FLUID IN SEVEN PATIENTS *

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During the last few years the appearance of several agents effective in the treatment of bacterial pulmonary infections has diminished the frequency of nontuberculous pleural space infection.[1] This condition still occurs, however, as a complication of some pneumonias, particularly in patients with a virulent infection in whom treatment has been delayed.[2]

Two features of the pleural cavity contribute toward making therapy of infections of the pleura more difficult than that of infections in many other sites. First, the ability of different drugs to pass into a collection of fluid or pus is quite variable; hence the question of whether the concentration of a given therapeutic agent which enters the pleural cavity after systemic administration is potentially effective must be answered for each drug. Second, there is a tendency to an early accumulation of large amounts of fluid or pus in this space in response to infectious processes, whereas the re-absorption of the proteinaceous material, and particularly pus, is minimal. This means that, even after the fluid is sterile, the problem of the elimination of the exudate is of considerable importance.

We are reporting our results, which demonstrate the ability of aureomycin † to penetrate into collections of fluid within the pleural and pericardial spaces in therapeutically adequate amounts, along with the results of treatment of nine patients with empyema, all of whom received aureomycin with or without other antibiotics. The aureomycin concentration in the body fluid was determined by a tube dilution method, using *B. cereus* as the test organism. Readings were made after four hours' incubation at 37° C. in a water bath.[3]

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† The aureomycin used in this study was furnished by the Lederle Laboratories Division, American Cyanamid Company, Pearl River, New York.

Results

Table 1 shows the concentration of aureomycin in 11 specimens of pleural fluid obtained from six patients. Twenty-four hours after the beginning of treatment a therapeutically significant amount of antibacterial activity was usually present. In general, the antibacterial action of the pleural fluid was 25 or 50 per cent of that in the blood, although in several instances it equaled that in the blood. Four specimens of pericardial fluid obtained from two patients gave similar results.

Certain clinical features of nine patients with empyema who were treated with aureomycin, with or without other agents, are shown in table 2. In

Table I

Relation of Serum Concentrations to Pleural and Pericardial Fluid Concentrations Following Oral Administration of Aureomycin

Patient	Duration of Therapy	Aureomycin Dosage (orally in mg.)	Time after Last Dose (hours)	Serum Concentration (mcg. per c.c.)	Concentration in Pleural Fluid (mcg. per c.c.)	Concentration in Pericardial Fluid (mcg. per c.c.)	Diagnosis
A. H.	3 doses 1 day 3 days 9 days 17 days	250 every 3 hr. 500 every 3 hr. 500 every 3 hr. 500 every 3 hr. 500 every 3 hr.	2½ 1½ 1 ½ 2½	1 4 4 4 8	0.02 0.25 0.50 0.50 2.0	—	Empyema (beta strep.). Bronchiectasis.
J. W.	2 days	500 stat. 250 every 3 hr.	2½	1	1.0	—	Pneumonia with pleural effusion. Pneumococcus Type IV.
J. Ha.	5 doses	250 every 3 hr.	3	0.5	0.04	—	Putrid empyema. Bronchiectasis.
J. Ha.	5 days	500 stat. 250 every 3 hr.	3	1.0	2.0	2.0	Polyserositis. Concato's disease. Pneumonia.
C. C.	10 doses 3 days 5 days 6 days	250 every 3 hr. 500 every 3 hr. 500 every 3 hr. 500 every 3 hr.	1½ 2½ 1 3	2.0 4.0 2.0 0.5	— — — —	— 1.0 0.5 0.25	Pneumonia. Tuberculous pericarditis.
W. B.	5 doses 7 days	250 every 3 hr. 250 every 3 hr.	2½ 3	0.5 0.5	0.25 0.5	—	Bronchiogenic carcinoma. Hydropneumothorax.
C. D.	8 days	500 stat. 250 every 3 hr.	1	4.0	2.0	—	Bronchiectasis. Pleural effusion. ? Carcinoma.

cases 1 and 5 the employment of aureomycin and of chest aspirations until fluid was no longer obtainable proved a quite successful form of therapy.

While aureomycin was effective in limiting pleural space infections in the case of several of the other patients, nevertheless, recovery was delayed because adequate drainage was not provided for. Thus symptoms subsided rapidly in case 2, but recovery did not occur until persistent fluid was found by x-ray and drainage was accomplished. Penicillin was added at the time aspiration was begun, so the rôle of aureomycin cannot be evaluated. Because of the large amount of cellular exudate in the pleural space, streptokinase and streptodornase were used to liquefy the fluid.

TABLE II

Result of Therapy with Aureomycin and Other Antibiotics in Nine Patients with Empyema

Pt. No. Age Sex Race	Contributory Conditions	Etiology and Type of Empyema	Treatment	Drainage	Course and Remarks
1. A. C. 62 M.C.	Pneumonia Bronchiectasis	Pneumococcus Type IV Nonputrid Nonencapsulated	Aureomycin, 250 mg. p.o. q3h from admission through 11th day.	Aspiration 1st day.	Temperature normal in 24 hours. WBC normal by 11th day. X-ray normal by 11th day.
2. J. H. 56 M.C.	Alcoholism	*H. influenzae* and *Streptococcus viridans* Putrid Encapsulated	Aureomycin, 250 mg., q3h first through 3rd day. Penicillin intrapleurally 100,000 U 2nd and 3rd day. Intramuscularly 1,000,000 U q2h 4th to 6th day. Procaine penicillin intramuscularly 300,000 U daily 8th to 28th day.	Aspiration daily 2nd to 14th days and every other day, 14th to 28th days. Streptokinase and streptodornase intrapleurally 7th to 16th days.	Temperature normal and symptoms better by 2nd day. Pleural fluid culture negative by 3rd day. Empyema pockets obliterated after repeated taps.
3. R. W. 24 M.C.	Alcoholism	*Staphylococcus aureus* Beta hemolytic streptococcus and *Streptococcus viridans* Nonputrid Encapsulated	Aureomycin 250 mg. p.o. q3h 1st to 4th day. 500 mg. p.o. q3h 4th to 10th day. Penicillin 500,000 U intramuscularly q2h 17th to 40th day; 100,000 U q3h 40th to 56th day. Intrapleurally 100,000 U every other day, 41st to 48th day.	Aspirations unsuccessful 2nd, 4th, 6th days; successful 17th, 20th days. Not pursued further. Surgical drainage 40th day.	Temperature normal and symptoms gone by 10th day; 7 days after, aureomycin discontinued (17th day); fluid rapidly increased while on penicillin and culture remained positive. Surgical drainage followed by defervescence and recovery.
4. E. H. 41 M.C.	Alcoholism *Klebsiella pneumoniae* pneumonia and bacteremia	Anaerobic paracolon intermediate Nonputrid but bronchopleural fistula present Encapsulation also present	Aureomycin p.o. 250 mg. q3h 1st to 55th day. 500 mg. q6h intravenously 2nd to 12th day. (2 doses chloramphenicol on 5th day.) Streptomycin intramuscularly 1 gm. q6h 6th to 12th day.	Aspiration 15th day. Water seal drain inserted 16th day and open drainage 23rd day.	Blood culture negative by 2nd day. Mental status good by 3rd day and temperature normal on 5th day. Suddenly became worse, probably due to development of bronchopleural fistula; fever 107° F. on 6th day. Then low fever until drainage established, followed by lysis and reexpansion of lung. Regional bronchiectasis.
5. A. H. 68 W.F.	Bronchiectasis	Beta streptococcus Nonputrid Encapsulated	Aureomycin 500 mg. p.o. q3h from admission through 29th day.	Aspiration 1st, 2nd, 4th, 9th, 13th, 18th days.	Temperature normal by 6th day. Chest fluid culture negative on 4th day. Decrease in amount on each tap. Recovery.

TABLE II—*Continued*

Pt. No. Age Sex Race	Contributory Conditions	Etiology and Type of Empyema	Treatment	Drainage	Course and Remarks
6. J. H. 54 M.C.	Pneumonia	Pneumococcus Type I Nonputrid Encapsulated	Aureomycin p.o. 250 mg. q6h from admission to 16th day; p.o. 500 mg. q3h 20th to 34th days and 45th to 62nd days. Penicillin intramuscularly 1,000,000 U q2h 34th to 45th days. Intrapleurally 100,000 U 36th day. Streptomycin, 0.5 gm. q12h 37th to 45th days.	Aspiration 36th, 37th, 40th, 43rd days. Dry on 47th day.	Temperature normal on 5th day; then followed low-grade course until arthritis of left knee developed on 20th day, with fever of 104° F. Two days after changing to penicillin, temperature spiked to 106° F. Repeated thoracentesis lowered fever but response was incomplete until aureomycin was used again; recovery followed.
7. R. N. 28 M.W.	Little's disease Pneumonia	Culture negative Nonputrid Encapsulated	Aureomycin, 250 mg. q4h p.o. 3rd to 29th days and 31st to 56th days. Procaine penicillin, 300,000 U intramuscularly q12h 29th to 42nd days.	Aspiration 3rd, 5th, 6th, 8th, 10th days and daily 12th to 18th days. Streptokinase and streptodornase 6th, 8th, 10th days and daily 12th to 28th days. Open thoracotomy 28th day. Revision on 95th day.	Patient had received large doses of penicillin, streptomycin, sulfonamides and intrapleural penicillin before admission. Patient remained chronically ill with no improvement until surgical drainage; eventual recovery.
8. J. F. 39 M.C.		Culture negative Nonputrid Encapsulated	Aureomycin, 750 mg. p.o. q6h 1st to 21st days. Procaine penicillin, 300,000 U intramuscularly daily 30th to 45th days.	Aspirated 4th day; unsuccessful five times between 6th and 21st days. Thoracotomy 30th day.	Patient had 9 days of intramuscular and aerosol penicillin before admission. Temperature became normal in 5 days on aureomycin and when repeated taps failed, he was felt to be cured. When relapse occurred, surgical drainage was followed by a cure.
9. W. M. 35 M.C.		Pneumococcus Type XIX Nonputrid Nonencapsulated	Aureomycin, 250 mg. p.o. q3h 1st to 7th days. Penicillin intramuscularly 1,000,000 U q3h 2nd to 15th days. Intrapleurally 100,000 U daily 2nd to 7th days.	Aspirated daily 1st to 7th days.	Temperature normal by 4th day. Rose for five days after discontinuing aureomycin; then recovery occurred.

Case 6 is also an example of a patient whose infection was incompletely controlled by aureomycin because of failure to remove the fluid from the chest. After repeated aspirations of empyema fluid, accompanied by instillations of penicillin, plus the use of penicillin and streptomycin by the intramuscular route, the temperature still persisted. Aspiration of the chest fluid was unsuccessful by this time, however, and the patient recovered completely on oral aureomycin alone when the therapy was changed back to that drug.

In patient 3, likewise, the infection was incompletely controlled because the encapsulated fluid could not be located. It appears in this case that the suppression of the infection with aureomycin was superior to that with penicillin, and that surgery had to be resorted to only because the purulent fluid could not be aspirated.

Patient 8 also responded well to aureomycin as far as symptoms were concerned, even though previous penicillin therapy had failed to control them. Because of failure to remove the fluid, however, relapse occurred and surgery was required to effect a cure.

Patient 9 was similar in that he was making what appeared to be a satisfactory response when, after the first thoracentesis, penicillin was substituted for aureomycin, because at that time the latter antibiotic had received very little trial in cases of empyema.

Patient 4 had an extremely difficult course. After a fair initial response to therapy of his Klebsiella infection, he developed a bronchopleural fistula and thereafter became extremely toxic. Surgical management, however, with aureomycin therapy, brought about recovery. Whether the bronchiectasis was present prior to the empyema or occurred as a complication of the Klebsiella infection could not be determined.

Patient 7 had chronic empyema at the time of admission despite previous treatment with penicillin and streptomycin and repeated aspirations. Aureomycin was the principal antibiotic used in conjunction with surgery; the patient recovered rapidly and completely.

The following two patients were treated with aureomycin as the sole antibiotic agent, and are therefore reported in detail.

Case Reports

Case 1. A. C., a 62 year old negro male, had been well until one week before admission to Gallinger Municipal Hospital, when he contracted an upper respiratory infection. Four days before admission he began expectorating teaspoonful amounts of brownish sputum. Two days before admission he had a shaking chill followed by fever. He had recovered successfully from another attack of pneumonia eight months previously.

On admission his temperature was 101.4° F. There was no respiratory distress. Diminished expansion of the left chest was present, with signs of fluid at the left base and moist inspiratory râles at the right base. The leukocyte count was 30,900 per cubic millimeter. A Type IV pneumococcus was cultured from a specimen of blood obtained on admission. A roentgenogram confirmed the presence of fluid at the left

base. The patient was immediately placed on 250 mg. of aureomycin orally at three hour intervals. During the first hospital day approximately 2.0 c.c of clear, thin fluid were aspirated from the left pleural cavity. A Type IV pneumococcus was grown from this fluid. All temperature readings subsequent to the admission elevation were normal, and the patient was asymptomatic by the third hospital day. At that time, signs of consolidation at the right base were noted, and the chest x-ray revealed pneumonia at the right base, with clearing of the fluid at the left base. Aspiration of the left chest at this time yielded no fluid. On the eighth hospital day, an x-ray revealed almost complete clearing of the pneumonia in the right base. The leukocyte count had returned to 10,700 per cubic millimeter on the eighth hospital day, and on the eleventh day was 7,000 per cubic millimeter. Aureomycin therapy was discontinued on the tenth hospital day and the patient was discharged on the fourteenth day, fully recovered.

Case 2. A. H., a 68 year old white female, had been diagnosed at another hospital and treated for progressive bronchiectasis four years before her present admission. Fatigue, anorexia, weight loss and chronic cough, productive of increasing amounts of thin, nonfoul green sputum had been present during the intervening years. Her cough increased one week before admission to the hospital and was accompanied by an increase in weakness, dyspnea, fever and left chest pain of a pleuritic nature.

On admission, the temperature was 103° F., the pulse rate 120 per minute and the respiratory rate 26 per minute. The patient was emaciated and pale, and appeared chronically ill. Her weight was 87 pounds. In addition to very pale mucous membranes, she had a smooth red tongue and a scaling erythematous rash on the extensor surfaces of the arms and hands. Auscultation revealed fluid at the left lung base and dry râles at the right lung base. There was a neutrophilic leukocytosis of 62,300 per cubic millimeter without other significant laboratory findings. A roentgenogram of the chest revealed consolidation and fluid at the left base. Oral aureomycin therapy, in doses of 500 mg. every three hours, was started. A thoracentesis the same day yielded 850 c.c. of cloudy fluid, from which were grown beta hemolytic streptococci (sensitivity to penicillin, 0.09 unit per c.c., and to aureomycin, 0.019 microgram per c.c.)

Thoracentesis performed on the two succeeding days yielded 235 c.c. and 170 c.c. of fluid, respectively, from which beta hemolytic streptococci were cultured. In subsequent thoracenteses at six to 10 day intervals, 25 to 50 c.c. of fluid were removed. These were sterile on culture. A maximal aureomycin concentration in the pleural fluid of 2 micrograms per cubic centimeter was reached on the seventeenth day of therapy, when the serum concentration was 8 micrograms per cubic centimeter. The patient improved gradually, and the fever remained within normal limits after 10 days of therapy. The blood leukocyte count, however, did not reach normal limits until a month had elapsed. Aureomycin therapy was discontinued after 32 days, by which time a total of 128 gm. had been administered. The patient was given intensive dietary and physical rehabilitation for the subsequent three weeks, until she was discharged from the hospital. Nine months later the patient was readmitted to the hospital and found to have pulmonary tuberculosis of both lungs, even though all examinations and cultures of specimens of sputum, chest fluid and bone marrow had yielded no evidence of tuberculosis during the first admission.

Discussion

The therapy of empyema has undergone revolutionary changes in the past 10 years. Prior to the advent of penicillin, recovery practically never occurred until surgical drainage had been established, and not always then. When penicillin was used in empyema caused by one of the gram-positive

cocci, especially in an early case, recovery could often be brought about by repeated aspiration of the empyema fluid, followed by intrapleural injections of penicillin. When surgical drainage was needed the prognosis was much better than in former times, because previous and concurrent penicillin therapy diminished the toxic effects of the infection upon the patient. This was particularly true in the case of putrid empyemas. Since penicillin, when administered systemically, penetrated so poorly into the pleural space, patients recovered only very rarely from empyema unless penicillin was instilled into the pleural cavity. In the case of empyemas caused by gram-negative rods, streptomycin could be administered in the same manner. Its administration was attended with the same limitations and, in general, produced comparable results.

Aureomycin possesses certain advantages over penicillin and streptomycin: (1) Its antibiotic spectrum is broader, and (2) it diffuses readily into the pleural space, as we have shown in table 1.

We employed aureomycin in the treatment of empyemas caused by pneumococcus, streptococcus, staphylococcus, *Hemophilus influenzae* and a paracolon organism. The two patients who received aureomycin alone had infections caused by a pneumococcus and a beta hemolytic streptococcus. They recovered completely without other treatment.

Five other patients (cases 2, 3, 6, 8 and 9) illustrate rather clearly the importance of removing the large accumulations of fluid from the pleural space in addition to using an antibiotic, even though the latter does penetrate the fluid in potentially effective concentration. In each of these cases there was a striking suppression of symptoms and signs of infection by aureomycin. In patient 3 this suppression of infection was superior to that obtained by large doses of parenteral penicillin, and in patients 6 and 9, to that obtained by a combination of large doses of parenteral penicillin and intrapleural penicillin. It appears, therefore, that aureomycin when accompanied by adequate drainage may be superior to penicillin in the treatment of these infections. It also seems likely that both patients 8 and 9 were lacking only the element of drainage to obtain a complete response to aureomycin. The use of penicillin in these patients was based on precedent rather than on failure of the aureomycin to exert a favorable effect.

Patient 7 illustrates the relative ineffectiveness of antibiotic therapy once the chronic stage of empyema is reached.

Aureomycin, therefore, appears to be an excellent therapeutic agent in the treatment of empyema if certain reservations are kept in mind. First, adequate drainage is necessary. If this is not assured relapses are likely to occur, as well as marked fibrosis of the pleura, leading to limitation of pulmonary function. The method of obtaining drainage does not seem so important as the necessity. If aspiration with or without streptokinase and streptodornase results in complete evacuation of the contents of the pleural cavity, this procedure will be as successful as thoracotomy. If the former

procedure produces incomplete results, the latter must be used. Aspirations of fluid in the case of aureomycin-treated patients are usually not needed so frequently as intrapleural punctures for the instillation of penicillin.

Second, the possibility that empyema may be present must be constantly borne in mind when treating pneumonia with aureomycin, since it is quite easy to miss this complication and thus lose valuable time in instituting aspiration before localization and organization of the exudate occur. In this respect aureomycin seems to offer more of a potential hazard than penicillin, since the dose of the latter usually employed for the treatment of pneumonia does not produce so complete a suppression of symptoms as the customary dose of aureomycin.

If these factors are given careful consideration, the use of aureomycin in preference to penicillin in the treatment of empyema would seem proper.

Summary

1. Nine patients with nontuberculous bacterial infections of the pleural space received aureomycin at some time during the course of treatment. Two patients recovered completely when treated with aureomycin and aspiration only. In five others, the antibiotic was felt to have a beneficial effect. In the remaining two patients it was impossible to evaluate the effect of aureomycin.

2. Aureomycin is a satisfactory antibiotic in the treatment of most bacterial infections of the pleural space provided adequate drainage is assured by repeated aspirations, with or without proteolytic enzymes, as indicated, or by thoracotomy.

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CASE REPORTS

EARLY GASTRIC SYPHILIS: REPORT OF CASE WITH EXTENSIVE INFILTRATION *

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THE subject of gastric syphilis appears to be in a controversial stage. Until recent years, authorities have almost unanimously stated that a luetic infection rarely involved the stomach. The pendulum is swinging, possibly to the other extreme. As Stokes, Beerman, and Ingraham [1] comment, one gets the "impression that syphilis of the gastrointestinal tract is an affair of everyday occurrence" from the multitude of reports appearing in the literature.

Probably the gastroscope has had a stimulating rôle in the increased interest in this subject. Since the report by Schindler [2] and the study by Sexton et al.[3] in 1937, numerous case reports have appeared in the literature describing the endoscopic appearance of the gastric mucosa in this disease. The studies in cases of early syphilis have been of particular interest, for it is in this stage that we have the least knowledge regarding any actual intrinsic pathology. The usual early appearance described [4] is that of "chronic superficial gastritis" or "gastric catarrh." Others [4, 5] report a visualization of atrophic gastritis and hypertrophic gastritis. In the latter stage, of course, ulcerating lesions, nodular lesions and infiltrating lesions are also seen.[4, 6]

The validity of diagnostic criteria has been debated pro and con, with well qualified observers taking opposing views. As might be expected, the pathologists usually require the most rigid set of rules for diagnosis. Boyd [7] still contends that syphilis of the stomach is a rare disease. He believes there is no diagnostic certainty except the demonstration of the *Spirochaeta pallida* in the involved tissue. Stokes et al.[1] also state that "the question of direct involvement of gastric mucosa in early syphilis is largely speculative." On the other hand, many clinicians agree with Eusterman,[8] who states that, although the clinical diagnosis may be inferential in a measure, it can be as accurate as the diagnoses in many other diseases. He says, "Physicians are willing to accept many cases of gastric and duodenal ulcer and carcinoma on the basis of characteristic history and the physical and roentgenological features, yet the hypercritical will not accept any case as that of proved syphilis without pathological confirmation. I feel that this attitude is not conducive to scientific progress and that it will jeopardize the lives

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of a certain group of patients afflicted with the type of lesion under consideration." After a fairly extensive study, Meyer and Singer [9] do not agree "that the final judgment should rest on microscopic changes, and that the macroscopic picture cannot be accepted as sufficiently clear-cut to permit even a preliminary diagnosis." Reynolds,[10] also quoting from Meyer and Singer's article, writes: "Special staining methods to demonstrate spirochaetes have a limited usefulness, both because of their capriciousness and because, as Singer has emphasized, contaminating mouth spirochaetes are indistinguishable from *T. pallida* in tissue sections."

We are not qualified to enter into the discussions centering about the manifestations and diagnosis of this condition. Recently, however, we have followed a case which has greatly stimulated our interest in the occurrence of early syphilis of the stomach.

Case Report

First Admission: A 35 year old white male college graduate was admitted to this hospital May 17, 1949, with complaints of nausea, vomiting, weakness and loss of weight. He stated that he had had occasional episodes of vague upper abdominal distress for a period of two years. There was no periodicity, no relationship to type of food or time of eating, and he got effective relief with the ordinary antacids. He lost no weight during this time. Three weeks before admission his acute symptoms appeared quite suddenly. The vomiting occurred without pain 10 to 30 minutes after eating. The vomitus always consisted of the food taken in the recent meal, and there was no evidence of retention vomiting. There was no hematemesis and no melena. At first the patient was unable to retain any solid foods, then his stomach rejected soft foods, and finally even liquids were emitted. He consulted his physician who, about a week prior to admission, had an upper gastrointestinal roentgen-ray study done. A duodenal ulcer was suspected and hospitalization was then recommended. During the three-week period, the patient lost 25 pounds.

In the family history, there was one brother with tuberculosis. The patient's past history was irrelevant, with the exception of a recent venereal infection. He had been married two years previous to this admission. The premarital serological tests for syphilis were done in this State on him and his prospective bride and were negative. He states that he had had no sexual contact with any woman except his wife until eight to nine weeks before hospitalization. At this time he stated that, while under the influence of liquor, he did have intercourse with a woman in another city. Five weeks after this, which was a little over three weeks before admission, he noted a penile sore which he described as being very superficial. He went to a physician who told him he need have no concern about it, and no blood test was done. It was about this time that he started to have his severe gastrointestinal symptoms.

Physical examination was essentially negative. There was noted a vesicular eruption on the fingers of both hands which he had had off and on for years. There was a small pea-sized lymph node in the left supraclavicular area. The blood pressure was 98 mm. Hg systolic and 52 mm. diastolic. The pulse was 68.

Laboratory Data: The urinalyses were normal. The hemoglobin was 15.75 mg. per cent, the red blood cell count was 4,960,000, and the leukocyte count was 7,400 per cu. mm., with 65 per cent neutrophils, 32 per cent lymphocytes, 2 per cent monocytes and 1 per cent eosinophils. The sedimentation rate was 18 mm. per hour (Cutler). The Kahn was positive, with a quantitative report of 2,048 units. The Kolmer complement fixation was 4 plus. The blood urea nitrogen was 8.5 mg. per cent and the total proteins were 6.72 gm. per cent, with 4.21 gm. albumin and 2.51 gm. globulin. The bromsulfalein test (5 mg. per kilo.) showed 4.6 per cent retention in 45 minutes. The thymol turbidity was 2.5 units. The cephalin flocculation was 1

plus in 24 hours, 2 plus in 48 hours. The icteric index was 5. The serum bilirubin was .62 mg. per cent. The total cholesterol was 242 mg. per cent, with 161 mg. per cent cholesterol esters. The spinal fluid examination revealed a clear and colorless fluid, with 13 leukocytes, 12 lymphocytes and 1 neutrophil. The smear was negative, the sugar was 48 mg. per cent, the globulin was 2 plus, the total proteins were 83 mg. per cent, the complement fixation was negative, and the gold curve was 0000000000. The gastric analysis revealed a total acidity of 11 units with no free HCl. After stimulation with 0.5 c.c. of histamine, the greatest total acidity was 37 units, with the highest free HCl of 12 units.

FIG. 1. Upper gastrointestinal x-ray, May 19, 1949.

The admission chest roentgen-ray showed no evidence of cardiac or pulmonary pathology. An upper gastrointestinal roentgenogram on May 19 was reported as follows: "A GI series disclosed no evidence of organic lesion of the esophagus. The stomach presented evidence of motor disturbance and alteration of shape. Gastric peristalsis was conspicuous by its absence. The pylorus remained open and the contrast medium made its exit from the stomach without the assistance of peristaltic action. Along the distal two-thirds of the lesser curvature of the stomach there was effacement of mucosal folds and on the opposite curvature exaggerated mucosal folds

were noted which could not be effaced by palpation. Roentgenograms of the stomach disclose complete absence of peristalsis and reveal a rigid appearance of the lesser curvature of the stomach which also presents fine serrations. They also demonstrate large rugae on the greater curvature side. No gross gastric ulceration was detected. The duodenal bulb was not deformed and presented no fluoroscopic or radiographic evidence of an ulcer niche. Roentgenograms made at one, five and 24 hour periods disclose a slight trace of gastric retention at the end of five hours at which time there is progress of the opaque meal to the hepatic flexure of the colon. The 24-hour roentgenogram reveals no gastric retention and discloses progress of the opaque meal to the distal portion of the transverse colon. No abnormality of the small bowel pattern is detected.

"*Impression:* The distal two-thirds of the stomach appears to be the seat of an infiltrating process of the linitis plastica type. This condition may be the result of gastritis associated with fibrosis of the walls but the possibility of a spreading type of carcinoma should seriously be considered. No evidence of duodenal ulcer was detected" (figure 1).

Subsequent to the above findings, this patient was seen by the consultants in Surgery, Dermatology and Syphilology, and Gastroenterology (E. C. R.). The consulting gastroenterologist expressed the opinion that this lesion was probably cancer and should be treated by resection as soon as the proper antiluetic treatment had been given. The chief of the Surgical Service also recommended surgery. It was agreed, however, that the patient be given antiluetic therapy, and on June 1 treatment with penicillin was started. Fifty thousand units were given intramuscularly every three hours. Within the first 24 hours, the patient experienced a marked increase of his nausea and vomiting. He had chills followed by fever and became very weak. The temperature rose to 101° F. The penicillin was continued and within a period of 48 hours these symptoms had completely disappeared.

A gastroscopy was done on June 8 and was reported as follows: "The gastroscope was passed easily. At no time were we able to identify the angulus. This would suggest that it had been ironed out by some process. The anterior wall of the stomach was pale and markedly stiffened. There was no abnormality of the mucosa in the form of erosions. The patient began to have marked retrograde peristalsis and the examination had to be discontinued. The body of the stomach was, therefore, the only portion of the stomach which was adequately examined.

"*Gastroscopic Diagnosis:* A nonspecific process probably involving the submucosal region of the stomach wall."

Penicillin was continued as above for a period of 15 days, making a total of 6,000,000 units. After five days of therapy, the patient felt that he was improved; his vomiting had ceased and he was beginning to feel hungry. The improvement continued rather rapidly and weight gain soon followed.

On June 24, the enlarged cervical lymph node was excised for biopsy. The microscopic sections showed no evidence of neoplasm and were reported as "inflammatory hyperplasia, moderate."

On June 29, the second gastroscopic examination was performed and was reported as follows: "The gastroscope was passed easily. At this examination, the angulus was identified. This was not identified on the last examination. The mucosa of the stomach appeared normal throughout. The antrum was seen only at its greater curvature and this appeared normal. No peristaltic waves, however, were seen to pass through this area. It seemed that the stomach at this time was more distensible as I was able to iron out the mucosal folds with air. Towards the posterior wall on the greater curvature there was an area which appeared paler and slightly lobular. This area, however, after careful study was not too far removed from the normal.

At the present time, from a gastroscopic standpoint, this stomach would have to be considered normal. I suggest that this man be re-x-rayed with careful comparison to the previous films for a complete reëvaluation of this case."

On July 1, a repeat upper gastrointestinal roentgen-ray study was summarized as follows: "Second examination of the upper gastrointestinal tract reveals that there has been considerable improvement in function of the stomach since first examination. The only abnormality noted is slight reduction in pliability of the gastric walls in the region of the pars media evidenced by shallow peristalsis in this region."

On July 8, the Kahn was reported as positive; the quantitative Kahn was 256 units; the complement fixation test was negative.

By July 15, the patient had gained nine pounds and it was decided to send him home for a leave trial.

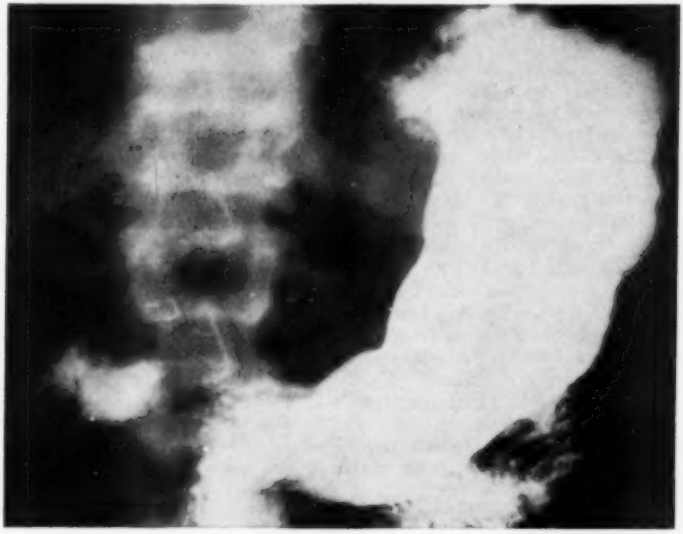

FIG. 2. Upper gastrointestinal x-ray, August 16, 1949.

Second Admission: On August 15, 1949, the patient returned from a 30 day trial at home. He stated that he felt well and had had no vomiting, and that his appetite was good.

An upper gastrointestinal roentgenogram was done on August 16, and the results were reported as being normal in all respects (figure 2). A gastroscopy was done on August 17, and the following is the report: "Gastroscope was passed relatively easily. The body of the stomach was examined in its entirety and was normal. An inadequate view of the antrum was obtained and nothing definite can be said about this area. On the posterior wall toward the greater curvature, approximately two-thirds towards the cardia from the pylorus, was a large rim of mucosa which appeared stiff. This fold was not seen at any other examination, and I do not know how to evaluate it. The remainder of the mucosa of the stomach appeared normal and the stomach was easily distensible.

"Gastroscopic Diagnosis: An inconclusive gastroscopic study."

At this time, the Kahn was still positive, with a quantitative report of 32 units. The complement fixation was negative. The fasting free gastric HCl was 0 with a response of 6 units after the use of histamine. The hemoglobin was 14.35 gm. per cent and the leukocyte count was 9,300 per cu. mm., with 54 per cent neutrophils and 46 per cent lymphocytes. The sedimentation rate was 9 mm. per hour (Cutler). The urinalysis was normal.

The patient was discharged from the hospital and advised to return in three months for a repeat checkup.

Third Admission: This man came into the hospital the third time on November 9, 1949, for reëvaluation. He was still asymptomatic, and stated that he had been eating everything while at home. He had been working rather strenuously and his weight had remained about the same.

The gastroscopic examination was reported as follows: "Gastroscope was passed easily into the stomach and the gastric angulus was identified. The gastric angulus was clear-cut and normal throughout. The gastric folds were easily ironed out with air.

"Gastroscopic Diagnosis: Normal stomach by gastroscopy."

The Kahn was positive, with a quantitative report of 16 units; complement fixation test was still negative. Blood studies and urinalysis were otherwise normal. The roentgenogram again reported no evidence of any abnormalities in the esophageal tract, stomach or duodenum.

In this case, our final diagnosis was early secondary syphilis, with submucosal infiltration of the stomach, the involvement including over two-thirds of the organ. Dr. John P. Scully, consultant in Dermatology and Syphilology, felt that probably there was also early asymptomatic neurosyphilis, basing his opinion on the cells and protein in the spinal fluid examination. He labeled the lesions of the hands epidermophytosis, and stated they had no relationship to the recent luetic infection. This rash remained unchanged.

This case, including all the films, was reviewed by the Gastroenterological Clinic at the Graduate Hospital, University of Pennsylvania, and they agreed that involvement of the stomach in this man was probably due to syphilis.

Discussion

We are aware of the numerous reports of syphilis of the stomach. In spite of this, it is our opinion that this case is of interest because of (a) the unusually early occurrence of a very extensive gastric lesion, and (b) the rapid return to clinical normality following therapy.

We quoted above a statement from Stokes et al. indicating their skepticism of early gastric lesions in syphilis. Bockus [9] writes in the most recent edition of his textbook: "There is little evidence to indicate that syphilis in its primary or secondary stages produces gastric symptoms of consequence." Most of the reports in the literature of early manifestations refer to mucosal changes as seen by the gastroscope or to microscopic cellular proliferation. The ulcerative lesions, the nodular lesions and the infiltrative lesions are generally accepted as occurring in the tertiary stage. In our rather extensive search, which we do not claim to be all-inclusive, we have found only one case reported in which a typically tertiary lesion occurred early. Reynolds [10] reported a rather convincing case of a 34 year old Negro who had had a penile lesion four weeks before the appearance of symptoms. The roentgen-ray picture eight weeks after the appearance of the lesion

revealed a stenotic lesion of the pylorus and antrum. This was before the advent of penicillin, and the response to antiluetic therapy was not too striking. Because of this, a laparotomy was performed and a biopsy obtained. The microscopic report stressed the marked perivascular cellular infiltration. Reynolds stated that there are two types of early gastric lesions: (1) superficial gastritis, a not uncommon lesion of little clinical significance, and (2) interstitial infiltration of the submucosa and muscularis of the stomach with thickening of the wall and stenosis of the lumen. This is very rare, and he calls it "precocious tertiarism." We feel that our case can probably be placed in this latter category.

In an infiltrative, invasive lesion of the linitis plastica type, it is usually assumed that there is marked fibrosis. Consequently, improvement under therapy is expected to be gradual, and frequently complete cure is not obtained. In our case, following a one-month period of therapy, there was no evidence of gastric disease visible by gastroscopy. The barium meal at this time revealed only a "slight reduction in the pliability of the gastric wall in the region of the pars media." The roentgen-ray and gastroscopic examinations 10 weeks after treatment was started revealed no evidence that any disease had been present. We do not see how any extensive fibrotic change could have been cleared up in this period of time. Some [4] claim that this is characteristic of this type of lesion, even in the latter stage. Others,[6, 11] however, refer to the permanent changes due to fibrosis following healing of the infiltrative lesions.

It is not assumed that the accuracy of diagnosis in this case will be unquestioned. If any other reasonable explanation can be offered for the sequence of events occurring in this patient, it would be of interest to us. The patient was an intelligent, educated man who understood our problem in diagnosis and made every effort to coöperate. Various members of the Medical Staff and the Consulting Staff checked and rechecked the history, with consistently uniform results. The relationship of onset of gastric symptoms to the initial lesion, the sudden rapid downward course, the initial upper gastrointestinal roentgenogram showing no abnormality in the stomach, followed in a very short period by the strikingly abnormal pattern, the unusually high Kahn titer, the Herxheimer reaction with onset of therapy, and the rapid and complete subjective and objective recovery with specific therapy cannot, in our opinion, be explained on any basis other than that of an early lues with extensive involvement of the stomach.

Summary

A case of gastric syphilis is reported in which an extensive linitis plastica type of lesion was discovered only nine to 10 weeks after exposure and four weeks after the appearance of the initial genital lesion.

Specific therapy with penicillin produced a complete subsidence of subjective symptoms and objective findings in a period of 10 weeks.

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A CASE OF MALIGNANT HYPERTENSION SECONDARY TO RENAL ISCHEMIA *

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THERE have been few reports of severe hypertension secondary to renal ischemia in which the ischemic kidney remained viable long enough to induce, by the elaboration of a pressor substance, generalized pathologic changes.[1, 2] In 1934, Goldblatt published the first account of experimentally produced hypertension in dogs secondary to renal ischemia.[3] Since that time, search for corroboration of this phenomenon in the human has not been entirely successful. There have been occasional reports of complete renal artery occlusion with associated hypertension of equivocal magnitude and duration.[4-7] In most of these cases, however, interruption of the renal blood supply was closely followed by complete infarction and early demise of the patient due to renal insufficiency.

The following case report presents a series of events which appear to resemble, more closely than has been heretofore reported, the original Goldblatt experiment.

CASE REPORT

A 43 year old white male clerk entered the neuropsychiatric unit of the Veterans Administration Center on December 13, 1948, complaining of extreme nervousness,

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weakness, insomnia, severe headache, occasional nausea and vomiting for the past two months. During the previous 24 hours, he had experienced paresthesias of the fingers associated with extreme weakness and shortness of breath.

The patient had been discharged from the Army in 1943 without medical complaint. He had drunk alcohol to excess for eight years but had abstained during the six months before admission. In October, 1948, he was admitted to a private hospital in Los Angeles because of persistent severe right flank pain with associated polyuria, nocturia and low-grade fever of one month's duration. Examination revealed a slightly elevated blood pressure (150 mm. Hg systolic and 100 mm. diastolic) and otherwise normal physical findings. Blood and urine examinations were normal, as were gall-bladder and gastrointestinal x-ray studies. Fluoroscopy of the chest showed the heart and aorta to be within normal limits, and there was no evidence of lung disease. A KUB x-ray satisfactorily outlined normal-appearing kidney shadows. There was no evidence of urinary tract disease. The patient remained in the hospital for 10 days and improved symptomatically before he was discharged. During the subsequent two months the right flank pain and polyuria continued to subside, but headache, low-grade fever, nausea and vomiting persisted. The day before admission to the neuropsychiatric hospital there was an extreme exacerbation of all symptoms except flank pain and polyuria.

Admission physical examination revealed a markedly apprehensive thin white male who appeared acutely and chronically ill. Temperature was 101° F., pulse, 135, respiration, 28, and blood pressure, 230/150 mm. Hg. Examination of the eyes showed normal light and consensual reactions. Funduscopic examination demonstrated normal discs, with narrow and tortuous arterioles, slight A-V nicking but no hemorrhages or exudates. The lungs were normal. The heart was not grossly enlarged. The rhythm was a regular sinus tachycardia. A grade 1 systolic murmur was heard at the apex. The liver was palpable 2 cm. below the right costal margin and was not tender to palpation. All reflexes were physiologic.

Admission urinalysis showed 4 plus albumin, a few white blood cells and many fine and coarse granular casts. Hemogram showed 5.6 million red blood cells, 116 per cent hemoglobin, 18,500 white blood cells with a normal differential count. Blood urea nitrogen was 17 mg. per cent and fasting blood sugar 129 mg. per cent. Urine concentration tests showed specific gravities from 1.018 to 1.024. Phenolsulfonphthalein excretion was 20 per cent in the first hour and 15 per cent in the second hour. Urea clearance was 72 per cent of normal. Repeat urinalysis on December 30, 1948, showed 4 plus albumin, five to 10 white blood cells, 10 to 15 red blood cells per high power field, and 50 to 75 fine and coarse granular casts per low power field. KUB x-ray indicated that the right kidney was approximately one-half the size of the left. There was no concentration of dye by the kidneys after intravenous injection of diodrast. Retrograde urography demonstrated blunting of the calyces of the right kidney, but visualization of the left kidney was inadequate. The injected phenolsulfonphthalein dye appeared in the ureteral catheters within 6 minutes on the left and 10 minutes on the right. The total dye excretion was 5 per cent in 15 minutes. Chest x-ray revealed a vertical heart of normal size. The lung fields were clear. Electrocardiogram was normal.

The patient continued to complain of headache, weakness, nausea, vomiting and extreme apprehension. About two weeks after admission he noticed blurring of vision. Funduscopic examination revealed marked blurring of the discs, with areas of hemorrhage in both retinae. At this time a spinal tap was performed which showed an initial pressure of 125 mm. of water, clear colorless fluid with a total protein of 94 mg. per cent, and a cell count of 2 red blood cells and 1 lymphocyte.

The patient was transferred to the medical service of the general hospital on January 3, 1949, with the diagnoses of malignant hypertension and possible cerebral

neoplasm. At the time of transfer he was complaining of weakness, paresthesias, abdominal discomfort and "clouded" vision. Blood pressure was 182/122 mm. Hg, temperature 98.6° F., pulse 96 and respirations 20. The pupils were dilated bilaterally, and papilledema of two to three diopters with hemorrhages was noted in both fundi. The heart was not enlarged to percussion, but the sounds had a tambour quality. There were occasional crepitant râles at the left midlung and lower lung field. The liver was enlarged 4 cm. below the right costal margin and was tender to palpation. The spleen was palpable 3 cm. below the left costal margin. There was no peripheral edema. Hemogram revealed 3.0 million red blood cells, 12,000 white blood cells, with a normal differential count and a sedimentation rate of 32 mm. per hour. Urinalysis showed 4 plus albumin, 3 to 4 red blood cells and 8 to 10 white blood cells per high power field, with occasional granular casts. The total protein was 5.0 gm., albumin 2.9 and globulin 2.1 gm. Blood chemical tests included a blood urea nitrogen of 28 mg. per cent, blood creatinine of 2 mg. per cent and blood chlorides of 458 mg. per cent.

Because of his severe hypertension, the patient was placed on a 200 mg. sodium diet. However, on this régime he rapidly became dehydrated. Blood chlorides fell to 434 mg. per cent and the blood urea nitrogen rose to 38 mg. per cent. A 24 hour urine chloride determination indicated an excretion of 2 gm. daily. The low salt diet was discontinued after the fifth day, and subsequent attempts to replace the blood electrolytes with sodium chloride and sodium bicarbonate solutions and salt tablets were unsuccessful. Throughout the remainder of the patient's illness the blood chlorides remained below 500 mg. per cent (normal, 570 to 640), despite attempted corrective therapy. Serum potassium varied between a low of 12.9 and a high of 15.6 mg. per cent. Therapy with oral potassium citrate had no effect. The blood pressure ranged from 240/160 to 182/122 mg. of Hg. The urine output varied from 500 to 1,500 daily, and contained from 4 to 7.5 gm. of albumin. The urine sediment continued to show 0 to 5 red blood cells, occasional white blood cells per high power field, with hyaline and granular casts. Repeat urine cultures were negative. The fundi continued to manifest bilateral papilledema. On January 13, 1949, the eye consultant observed cotton wool exudate, flame-shaped hemorrhages and attenuation of the arterioles.

On January 21 the patient began to display signs of congestive failure, including râles at the lung bases, sacral and pedal edema, high venous pressure (200 mm. of water) and prolonged circulation time (24 seconds, arm to tongue). A chest x-ray at this time showed a right pleural effusion and a diffuse mottled interstitial infiltration extending from the hilum into the left midlung field, with a similar process involving most of the right lung. The heart now appeared moderately enlarged. The patient's temperature rose to 102° F., and he developed a cough productive of a small amount of blood-streaked sputum. The course remained febrile despite antibiotic therapy. In addition to paresthesias, the patient now began to exhibit marked weakness of both lower extremities, with absent deep reflexes, positive Babinski signs and fecal and urinary incontinence. Another spinal tap revealed a pressure of 190 mm. of water, normal dynamics and clear, colorless fluid. The total protein was 40 mg. per cent and 3 lymphocytes per cubic millimeter were found. Other laboratory data included a blood urea nitrogen of 60 mg. per cent, creatinine of 5 mg. per cent, blood uric acid of 12 mg. per cent, blood sodium chloride of 498 mg. per cent, CO_2 combining power of 54 vol. per cent, blood calcium of 10.5 mg. per cent, inorganic phosphorus of 3.7 mg. per cent, and blood sugar of 116 mg. per cent. Hemogram showed 2.9 million red blood cells and 21,000 white blood cells. Electrocardiogram now indicated a first degree A-V block with no evidence of myocardial infarction.

The course continued downward, with progressive weakness and emaciation. The temperature remained elevated, and the chest x-ray showed progression of the pulmonary lesions. In spite of an adequate urinary flow, progressive renal failure

ensued, as indicated by rising creatinine and blood urea nitrogen (126 mg. per cent on February 1, 1949). The patient died February 19, 1949, five months after the onset of his illness.

Autopsy Findings: The primary pathology in this case was found in the kidneys, but there were related significant changes in the heart and lungs.

It was noted at the time of autopsy that two renal artery ostia were present on each side of the aorta (figure 1), one larger than the other. The two arteries supplying the left kidney were patent. The larger of the right renal arteries, which was distributed to the upper and midportions of the right kidney, however, contained an occlusive organizing luminal thrombus. This thrombus extended to the renal pelvis, where the lumen again became patent. The smaller right renal artery, distributed primarily to the lower pole, was entirely patent.

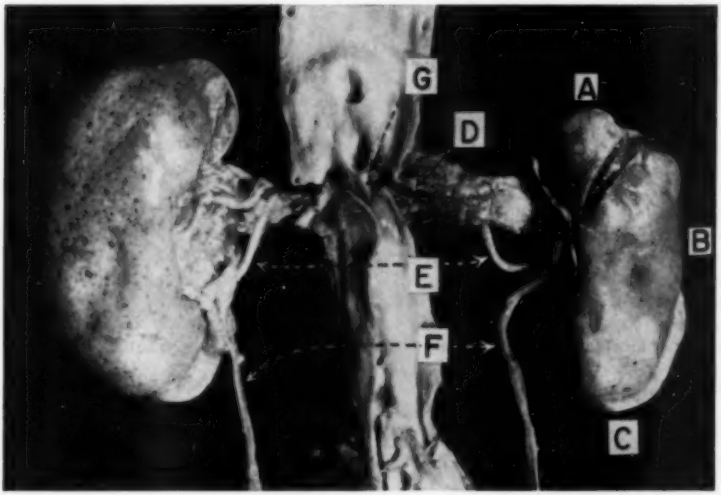

FIG. 1. A. Zone of infarction. B. Zone of atrophy. C. Zone of malignant nephrosclerosis. D. Thrombus in right renal artery. E. Accessory renal artery to lower pole. F. Ureter. G. Ostium of accessory renal artery.

The kidneys weighed 300 gm., although the right kidney was half the size of the left. The capsule of the larger left kidney stripped with ease, revealing a finely granular, mottled, pale-yellow renal surface on which numerous petechiae were seen. The capsule of the smaller right kidney was stripped with some difficulty, as it was adherent to the renal cortex at the middle and upper thirds. The cortical surface of the lower pole of the right kidney had petechiae and a pale yellow, mottled appearance, precisely the same pattern as the entire cortical surface of the left kidney. The remaining cortical surface of the right kidney, including the upper pole, was slightly depressed below the level of the lower pole, and appeared smooth and brown in color. In the region of the upper pole, a 1 by 2 cm. triangular, yellow-white scarified infarct was seen. The parenchyma of the left kidney, on section, revealed a visible corticomedullary demarcation. The demarcation line between the cortex and medulla of the right kidney, on section, was indistinct except in the region of the lower pole.

Microscopic sections taken from the enlarged left kidney showed scattered arteriolar disease varying from marked intimal proliferation to smudgy hyaline arteriolar necrosis, which involved the glomerular tufts in some instances (figure 2). The glomerular disruption varied from frank necrosis, associated with arteriolar necrosis of the tributary arteriole, to varying degrees of acute glomerular swelling and fibrosis. Some glomeruli were reduced to small balls of scar tissue within Bowman's capsule. Similar arteriolar necrosis was noted in most of the systemic ar-

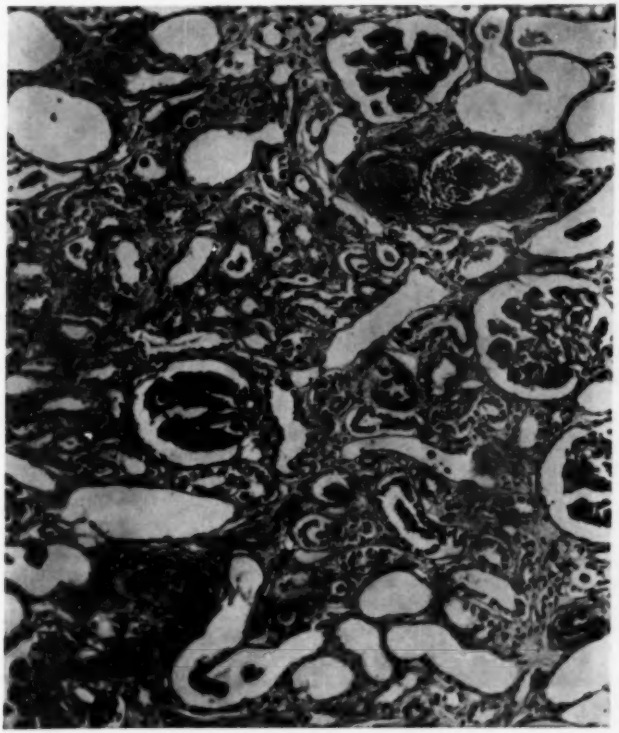

FIG. 2. Section of left kidney exhibiting advanced malignant nephrosclerosis. Description in text.

terioles as well, including arterioles of the gastrointestinal tract, adrenal glands, lungs and pancreas.

Microscopic sections from the smaller right kidney revealed normal appearing glomeruli in an almost homogeneous matrix of markedly atrophic tubules whose lumina were minute or nonexistent (figure 3). A survey of the arteries and arterioles revealed no evidence of arteriolosclerosis or necrosis. However, sections of the right kidney at its junction with its lower pole showed a sharp transition to the microscopic appearance of sections taken from the left kidney.

The heart weighed 500 gm. and exhibited primarily a left ventricular hypertrophy. The foramen ovale was patent and admitted a large size probe.

The lungs were grossly normal in size and appearance except for two small areas of infarction. In the periphery of the right middle lobe a firm, gray-white area, 2 cm. in diameter, was noted. Microscopically, this proved to be an area of necrosis showing minimal marginal organization. The peripheral portion of the pulmonary artery supplying this lobe was occluded by an adherent gray-red thrombus. On the lateral margin of the left lower lobe, a firm 2 by 4 cm. wedge-shaped hemorrhagic infarction

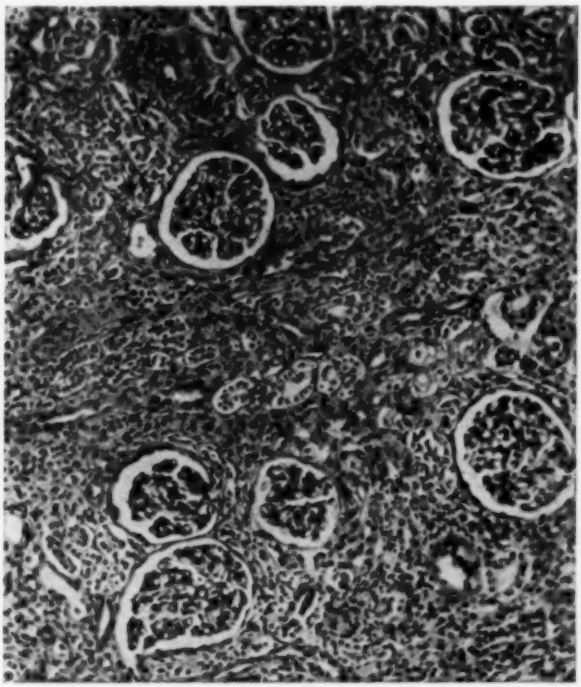

FIG. 3. Section of right kidney showing marked atrophy. Description in text.

was noted. Proximal to this area, the subtending pulmonary artery branch was occluded by an attached gray-red thrombus.

Additional findings included numerous areas of focal hemorrhage throughout the mucosa of the entire gastrointestinal tract, and multiple organizing thrombi in the periprostatic venous plexus.

COMMENT

By correlating the clinical and pathologic data presented, it is possible to trace the course of events in this case. It may be assumed that the initial symptom of right flank pain, followed by polyuria, represented embolic occlusion of the main

right renal artery. Except for a small area at the upper pole, infarction of the kidney did not occur because of the minimal collateral circulation sustained by a small accessory renal artery. However, the small amount of blood supplied by the collateral circulation to the remainder of the right kidney was inadequate to maintain normal tissue function, and a relative ischemia of this tissue developed. As a result of circulatory impoverishment, the renal parenchyma gradually developed atrophic changes. Concomitantly, sufficient pressor substance was elaborated by the ischemic tissue to maintain and sustain a severe hypertension, which rapidly progressed to the malignant phase. Clinically, it would seem that the ischemia and subsequent renal atrophy preceded the development of hypertension. Certainly the atrophic portion of the kidney exhibited no evidence of vascular disease, whereas the lower pole and the entire left kidney showed all the pathologic changes associated with malignant hypertension.

Although the antemortem diagnosis was not made in this case, in retrospect, evaluation of certain investigative procedures prior to the onset of renal failure might have given valuable clues to the basic pathology. A more satisfactory therapeutic approach, such as nephrectomy, might then have been considered. An early intravenous pyelogram showing unilateral function combined with renal arteriography would have given conclusive information. Later, retrograde pyelography, showing unilateral renal atrophy as well as differential renal function, would have given additional corroboration.

This case represents a combination of features uniquely similar to Goldblatt's experimental work on the pathogenesis of hypertension. No attempt will be made to explain or correlate the numerous other clinical and pathologic aspects.

Summary

A case of malignant hypertension secondary to renal ischemia is presented, in which the clinical and pathologic features are strongly suggestive of a "Goldblatt mechanism."

Acknowledgment

The authors wish to express their appreciation to Dr. Leo Kaplan, Chief of the Laboratory Service, Wadsworth Hospital, Veterans Administration Center, Los Angeles, California, for his generous counsel and assistance.

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TREATMENT OF BROMISM WITH THE ARTIFICIAL KIDNEY *

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THE high incidence of chronic bromide intoxication has been repeatedly stressed in the literature.[1, 2, 3, 4, 5] The presence of bromide in proprietary remedies which may be sold without prescription particularly lends itself to the prevalence of this clinical condition. Bromides in small doses cause sedation; in high doses, or with continued intake exceeding excretion, chronic poisoning may occur, in which mental and neurologic disturbances are the most prominent features. Delirium, hallucinations, confusion and disorientation may be present in severe cases.

The metabolism of the bromide ion is much like that of the chloride ion and, in a sense, the renal tubules cannot distinguish between the two. Indeed, it has been stated that the kidneys have less ability to excrete bromide than chloride.[6, 7] Palmer and Clarke [8] found that the percentage of bromide of the urinary halides is lower than that of the blood halides, although others [9] do not feel that this occurs. It is a well known clinical fact, however, that the excretion of bromide occurs extremely slowly. This is particularly true when the patient has a low intake of sodium chloride during the period of bromide ingestion. Palmer and Clarke [8] found that 97 mM. of bromide injected into a 15 kg. dog on a low salt diet was reflected four and one-half months later by a blood bromide level of 2 mM. per liter. Conversely, the excretion of bromide can be hastened by the ingestion or infusion of chloride containing salts, and, indeed, this forms the basis for therapy.

Both bromide and chloride ions occupy an extracellular position [10] with the exception of the red blood cells, which may contain large amounts of both. Indeed, the volume of distribution of bromide has been suggested as a measure of extracellular fluid volume,[11] although recent evidence indicates that the measurements obtained are greater than the actual extracellular space.[12]

The severity of the clinical syndrome of bromide intoxication and the slow excretion of bromide even with sodium chloride therapy make a more rapid method of treatment desirable. The small molecular weight of the bromide ion (approximately 80) and its predominantly extracellular position suggested the possibility of rapid removal of bromide ions from the plasma and extracellular fluid by the artificial kidney. In this situation, the rate of removal of bromide would be a function of its diffusion gradient from blood to bath, across an inert cellophane membrane which is easily permeable to this ion. The removal of other toxic diffusible substances by hemodialysis has already been accomplished [13, 14] in the case of the barbiturates and aspirin. The efficacy of this type of therapy and the degree of safety with which it may be accomplished [15] make the use of the artificial kidney feasible under these circumstances.

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From the Medical Service, Peter Bent Brigham Hospital, and the Department of Medicine, Harvard Medical School.

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Case Report

A 53 year old housewife had allegedly taken Bromo Seltzer intermittently for 30 years. In 1943 she had been hospitalized for the treatment of bromism. Her behavior was somewhat irregular, and she drank alcoholic beverages to excess. Because of headaches, increasing nervousness and agitation, she allegedly took Bromo Seltzer daily for two months prior to admission. With the onset of an upper respiratory infection, she developed confusion and paranoid ideas and was hospitalized. It was reported that her serum sodium bromide level was "over 300 mg. per cent" (29.1 mEq. bromide per liter). She was treated for one week with infusions of sodium chloride and with oral salt. There was little change in the psychic disturbances. She was transferred to the Peter Bent Brigham Hospital on March 29, 1951. Physical examination at this time showed a poorly oriented white female having paranoid ideas. The blood pressure was 178/110 mm. of Hg. No skin rash was present. There was a grade I aortic systolic murmur and early sclerosis of the fundal arteries. The blood Hinton test was negative. The hematocrit was 47. The serum bromide level was 21 mEq. per liter. Blood urea nitrogen was 14 mg. per cent. The urine showed 1 plus protein. An x-ray film of the chest revealed the heart and lungs to be within normal limits. An electrocardiogram was considered characteristic of left ventricular hypertrophy.

On the second hospital day, hemodialysis on the artificial kidney was carried out for five hours. The rate of blood flow through the apparatus was 200 c.c. per minute. During the procedure there was no change in the patient's disorientation and confusion. Four hours after dialysis, however, there was improvement in her mental status. The following day she was calm, lucid and oriented. There was complete amnesia for the period of 10 days to two weeks before admission, and she remembered nothing of the treatment with the artificial kidney. She remained well except for nausea and vertigo, which persisted for four days, and she had no further evidence of toxic psychosis.

Discussion

This case illustrates the ease with which bromide intoxication may develop. Because of headaches and nervous symptoms, the patient repeatedly took Bromo Seltzer. This preparation contains, according to the label, 5 gr. of sodium bromide (3.2 mEq. of bromide) in "each heaping teaspoonful." As bromism gradually occurred she became increasingly more agitated, and took more Bromo Seltzer in an attempt to obtain relief, until a toxic psychosis existed. It was only then that the diagnosis of bromide intoxication was made. This vicious circle of bromide ingestion to relieve the symptoms of bromism has been stressed,[9] as has the potentiation of toxicity by malnutrition and arteriosclerosis.[8] In this patient, an upper respiratory infection which contributed to the inadequacy of the dietary intake and thus of chloride intake undoubtedly enhanced the syndrome.

The patient's serum bromide level was over 300 mg. per cent (29.1 mEq. bromide per liter) when she was first hospitalized. Levels of 200 mg. per cent of sodium bromide (19.4 mEq. bromide per liter) are a strong indication of bromide intoxication, although there is no absolute correlation between the symptoms and the blood bromide level.[16] The patient's serum halide level on admission to the Peter Bent Brigham Hospital was 114 mEq. per liter (done by the method of Schales and Schales [17]), and the serum bromide level was 21 mEq. per liter (done by a modification of the method of Wuth [18]). The slightly elevated serum

halide level may have been due to hemoconcentration and possibly to prior treatment with saline.

Hemodialysis by the artificial kidney for five hours resulted in a rapid lowering of the serum bromide level from 23 mEq. per liter to 3.3 mEq. per liter. This is in marked contrast to the relatively slow decrease in the serum bromide level which occurs during the usual course of therapy with sodium chloride.[4] These comparative data are shown in figure 1. During dialysis, a total of 166 mEq. of bromide ion was recovered in the dialysate bath.

The dialysate bath contained 129 mEq. of chloride ion per liter and 140 mEq. of sodium ion per liter. The diffusion gradient of bromide ions was from blood to bath; that of chloride ions, from bath to blood; and there was essentially no gradient for sodium ions. Thus the replacement of bromide ions present in the serum and extracellular fluid by chloride ions was facilitated, while at the same time the danger of increasing the extracellular fluid volume was not present. This circumvents a complication of the usual therapy with sodium chloride in patients having cardiac or renal impairment. The high concentration of chloride

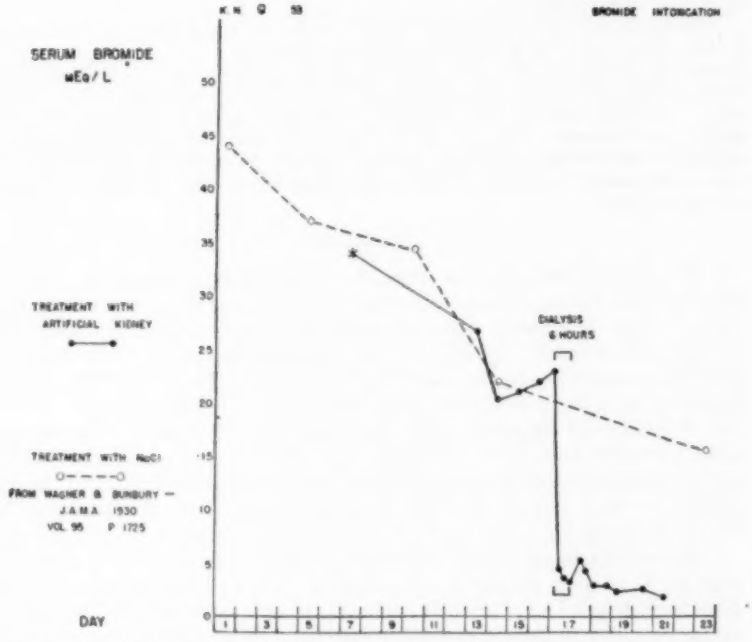

FIG. 1. The blood bromide levels in this case follow roughly those found by Wagner and Bunbury during sodium chloride treatment. On May 31 the patient was treated by hemodialysis on the artificial kidney. Serum values at the beginning (0 hr.) and end (5 hr.) of the figures are given. The marked difference accomplished by dialysis is apparent. Samples drawn 4 and 8 hours after the procedure, but on the same day, showed a slight increase in bromide level.

ion in the bath also results in increasing the serum chloride ion concentration and the total serum halide concentration in spite of the diminution in serum bromide concentration. This should promote the renal excretion of any bromide remaining after dialysis. It has been stated that the administration of chloride with a disposable cation is more effective in promoting bromide excretion than is treatment with chloride combined with sodium.[19] This is essentially what occurs during dialysis in which there is a bath-to-blood gradient for chloride and none for sodium. These predialysis and postdialysis values of the serum and urine chloride and bromide concentrations are shown in table 1.

TABLE I

Date	Serum		Urine		
	Total Halide (mEq./L.)	Bromide (mEq./L.)	24 Hr. Vol. (ml.)	Total Halide (mEq./L.)	Bromide (mEq./L.)
Mar. 29	114	21	520*	109	14.0
Mar. 30		22	1,180	60	7.2
Mar. 31	0 hr. 115	23	520	110	
Mar. 31	5 hr. 130	3.3			
Apr. 1	126	2.9	400	91	5.9
Apr. 2		2.4	260	49	5.3
Apr. 3		2.5	700	46	4.0
Apr. 4		1.7	1,180	37	3.6

* 10 hr. volume.

Other than nausea and some vertigo, which persisted intermittently for four days following hemodialysis, there was no evidence that the rapid lowering of the bromide level was harmful. This is of importance, since it has been said that vigorous treatment of bromism may be harmful and that the period of treatment must necessarily be prolonged to prevent toxic reactions. In all probability, part of this effect may be due to the rapid infusion of large amounts of sodium chloride, particularly in patients with cardiovascular or renal disease. Wagner and Bunbury [4] state that "rapid infusion of sodium chloride may result in a rise in serum bromide level as chloride displaces bromide from the tissues." Others, however, have not found this to occur,[6, 19] and since a relatively small amount of bromide is present in the intracellular space it is probable that this explanation is invalid. In any case, the rapid removal of bromide by the artificial kidney resulted in no deleterious effect other than slight nausea and vertigo.

SUMMARY

A case of bromide intoxication has been treated by hemodialysis with an artificial kidney. There were a rapid lowering of the serum bromide level during dialysis and a prompt clinical improvement immediately following dialysis. Hemodialysis is a rapid and effective therapeutic procedure for bromism.

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THROMBOCYTOPENIC PURPURA FOLLOWING QUINIDINE THERAPY *

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UNTIL most recently, thrombocytopenic purpura occurring during the administration of quinidine was unknown. The fact is well established that its levorotatory isomer, quinine, and related levorotatory compounds, ethylhydrocupreine and cinchonidine, can produce idiosyncrasy,[1] and especially that quinine can be the cause of suppression of blood platelets with consequent hemorrhagic

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manifestations.[2, 3] It had been generally assumed that their dextrorotatory counterpart was singularly incapable of producing toxic manifestations.

Subsequent to Broch's report in 1941 of a case of thrombocytopenic purpura during quinidine therapy,[4] the world literature is completely free of reports until a report in 1947 by Soisalo of a similar case.[5] Since then a number of single case reports have appeared.[6, 7, 8, 9] The following case is the seventh (the first in a male) to be so reported.

Case Report

A 65 year old white male house painter, a Russian, was first seen on April 3, 1950, with the complaint of weakness of two weeks' duration. The past history was entirely noncontributory. Having always been in good health, the patient had never previously consulted a physician. Systemic review of complaints revealed only an occasional headache.

The onset of the present illness had been gradual. The patient noticed that he was weak, especially while working. At the onset, feeling that he had some fever, he had self-diagnosed "grippe" but had taken no medication. Finally, he was so greatly troubled by the feeling of weakness that he consulted a physician.

Physical examination revealed an elderly male who appeared acutely ill. The blood pressure was 140/90 mm. Hg. The pulse was grossly irregular, with an average rate of 80 per min. There was no exophthalmos. The ocular fundi revealed some narrowing of the arterioles, but no hemorrhages or exudates. The ears were normal. The mouth revealed very poor dentition, with almost complete edentia. No

Table I

Prothrombic Activity

Plasma Dilution	Time	Per Cent	Control
100%	17 sec.	68%	15 sec.
50%	23 sec.		18 sec.
25%	30 sec.		24 sec.
12.5%	45 sec.		40 sec.
Bleeding time (method of Duke)		13 minutes	
Coagulation time (method of Lee-White)		18 minutes	
Clot retraction		Incomplete at 10 hours	
Character of clot		Friable	
Tourniquet test		Strongly positive	

dentures were used. The remaining teeth showed extensive caries. There was no "lead line." There was no abnormal filling of the neck veins. The lungs were clear. The heart revealed auricular fibrillation; there were no murmurs. The abdomen was normal; the spleen and liver were not palpable. The extremities were normal. There were no petechiae or ecchymoses. The hemoglobin was 14.5 gm. and the urinalysis was negative. Fluoroscopy of the heart revealed what appeared to be paradoxic pulsation at the lower portion of the left border, but the heart was otherwise normal in size and shape. The electrocardiogram confirmed the clinical findings of auricular fibrillation and showed, in addition, periods of flutter. The patient was placed on quinidine sulfate, 0.2 gm. three times a day, and phenobarbital, .015 gm. four times daily. After an interval of four days, the fibrillation had reverted to regular rhythm. Quinidine was therefore cut to 0.2 gm. twice a day. However as the patient reverted to the flutter-fibrillation within a week, the quinidine was increased to 0.2 gm. four times daily. That night he suffered an episode of syncope but the rhythm remained abnormal, although the following day it was found to have returned to normal. An electrocardiogram confirmed this but revealed an abnormality in the P waves for the first time. These were broad and notched, with evident depressed P-R segments in all

TABLE II
Hemogram

Date	Hgb(%)	RBC	WBC	Bands	Polys.	Eos.	Bas.	Lym.	Monos.	Thrombocytes
6/12/50	85	4.30	7,800	6	66	0	0	24	4	36,000
6/17/50	74	3.88	6,550	5	65	0	0	25	5	50,000
6/19/50	76	3.90	8,500	3	63	0	0	29	5	54,000
6/21/50	71	3.84	5,300	3	61	0	1	31	4	50,000
6/23/50	82	4.07	6,500	5	50	0	0	38	1	112,000
6/29/50	88	4.37	6,500	3	57	0	2	33	5	226,000

leads. It was felt that he had possibly suffered an auricular infarction or, as an alternate possibility, that the P wave changes were of the type described as "prefibrillatory."

The patient was placed at complete bed-rest at home for the following four weeks. During this time, quinidine was continued in a dose of 0.2 gm. three times daily. The rhythm of the heart remained normal. Throughout the entire period of bed-rest, however, it was noted that the patient was dull and lethargic, and frequently somnolent and uncommunicative. At the time there was no explanation for these symptoms, and they were thought to be due to the mental depression over a disabling illness, so frequently seen in a previously active man. It is now felt, however, that they could have been due to some cerebral involvement, such as petechiae. During the last week of bed-rest he began to complain of pain in the legs and feet. Examination revealed them to be covered with a petechial and purpuric eruption up to the knees. There were showers of petechiae over the rest of the body. Up to this episode the patient had been on quinidine for about nine weeks, with a total dosage of about 24.0 gm. In retrospect, it was recalled that he had been complaining of bleeding from the gums for some days, but that the complaint had been brushed aside as being due to very badly infected mouth and gums. However, at this point quinidine was stopped and a hematologic work-up performed.

A bone marrow study was made, using the right iliac crest to aspirate approximately 0.3 c.c. of marrow. The total nucleated count was 31,000 per cu. mm. There was a mild myeloid shift and the myeloid-erythroid ratio was 1.5 to 1. The

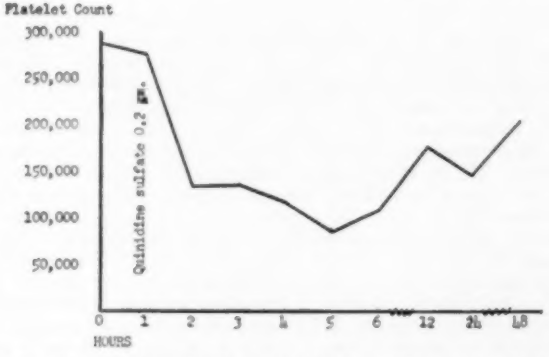

FIG. 1. Effect of a test dose of 0.2 gm. of quinidine sulfate on the platelet count.

megakaryocytes were not increased in numbers. Their cytoplasm was of varying shades of blue, and most showed poor granularity. There was no margination of the thrombocytes. Occasional megakaryocytes showed a light bluish-staining clear area, resembling a membrane.

Examination of the blood is reported in the attached tables. It will be noted that the thrombocyte level of 36,000 rose to normal 17 days after withdrawal of the drug. The patient was placed on ascorbic acid, 1,000 mg. daily, and ephynal acetate, 150 mg. daily. There was progressive recovery in the ensuing several weeks, and rapid loss of the previous lethargy.

After it was demonstrated that the thrombocyte count had been stabilized in the normal range for some time, a thrombopenic test was attempted to establish quinidine as the causative agent. Accordingly, two control counts were performed, an hour apart; then 0.2 gm. of quinidine sulfate was given orally. In one hour the thrombocyte count dropped 50 per cent. In four hours it was down to 90,000 from a control level of 280,000 (figure 1). There were no clinical manifestations of purpura, gingival bleeding or lethargy.

Discussion

The present case is the seventh to be reported (the first in a male) of thrombocytopenic purpura following the administration of quinidine sulfate. As in most of the previously reported cases, a test dose given after a suitable control period resulted in a return of the thrombopenic state.

Ordinarily, thrombocytopenic purpura can be classified into either a primary or a symptomatic group. The symptomatic group can occur in association with other primary disturbances of the blood or following exposure to chemical, vegetable, animal or physical agents. That the disorder can follow promptly after exposure, or slowly during repeated exposure, is suspected; however, it is difficult without following the thrombocytes to be certain of the time at which such a decline occurs. Although the critical level of thrombocytes is supposed to be 50,000 per cu. mm., it is doubtful whether such is always true. There is a vascular phase which is independent for the most part of the thrombopenic phase, and which may subside almost completely. The change may occur rapidly, as in Nudelman's case, where bleeding developed quickly after administration of the drug.[6] In our case, no bleeding occurred even though the thrombocytes fell to a level of 90,000. However, the dose given was small and only at one time, and it is very likely that the continued administration of the drug would have resulted in a return of all the previous manifestations, the gingival bleeding and the purpura. This strongly suggests that the drug acts directly on the circulating thrombocytes. It is doubted that the drug accelerates the normal splenic destruction of thrombocytes, as it would seem that such an effect could not occur so rapidly, requiring as it does the mediation of that organ. It is felt that, in spite of previous concepts to the contrary, quinidine will have to be indicted along with its levorotatory isomers as being capable of producing toxic manifestations. Therefore, all cases of quinidine should be checked by platelet counts to be certain that such toxic changes are not occurring.

Summary

A case is presented of thrombocytopenic purpura which followed the administration of quinidine sulfate. After hematologic and clinical recovery, a

test dose of quinidine reproduced the hematologic picture in a matter of two to four hours. A warning is sounded that this might not be a great rarity, and that therefore all cases on quinidine should be carefully observed from the hematologic standpoint.

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COMBINED AUREOMYCIN AND STREPTOMYCIN THERAPY OF *PSEUDOMONAS AERUGINOSA* (*BACILLUS PYOCYANEUS*) MENINGITIS, WITH A CASE REPORT*

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INTRODUCTION

THE following case of *Pseudomonas aeruginosa* (*Bacillus pyocyaneus*) meningitis following radical surgery for carcinoma of the external auditory canal is presented because of the relative rarity of meningitis due to this organism, and because of the excellent response to a combination of antibiotics, including streptomycin and aureomycin.†

CASE REPORT

A 64 year old white widow was admitted for the first time to the Otolaryngology Service of the Presbyterian Hospital with a four and one-half month history of severe

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occipital headache radiating to the right ear. There was a 50 year history of a chronically draining right ear. There had been attacks of bilateral otitis media in childhood, but the left ear had been dry for the last 40 years. There had been no serious illnesses, and there was no history of diabetes or cardiac or renal difficulties.

Examination showed a granulating mass almost entirely filling the right ear canal; biopsy revealed granuloma of the right middle ear. The patient had been admitted because of extreme dizziness and vertigo, with a questionable predilection for falling to the right, which had been present for from four to six days.

Physical examination revealed obvious severe hearing loss, a granulating mass of the inner one-third of the right ear canal, and a thickened, scarred, retracted left tympanic membrane. Patient was afebrile, showed no signs of meningeal irritation and had no cervical adenopathy. Significant laboratory findings included an essentially normal blood count and 1 plus glycosuria, with a fasting blood sugar of 225 mg. per cent. Mastoid x-rays showed bilaterally sclerotic mastoids. Two cultures from the right ear revealed gram-positive diplococci overgrown with *Ps. aeruginosa* (*B. pyocyaneus*). A second biopsy of the granulating mass of the right ear was reported as squamous cell epithelioma.

Course: The patient became febrile for four days following the admission biopsy and was placed on 400,000 units of procaine penicillin daily, with a prompt defervescence. Operation was performed on the tenth hospital day and consisted of a radical mastoidectomy with excision of the skin of the right external auditory canal. The polypoid mass was found to extend into the middle ear. The dural plate was partially missing over the labyrinth, and thickened dura was found at this point. Extensive surgery was required to effect complete excision of the tumor, and this necessitated removal of more of the dural plate. The tumor appeared to have been completely excised.

The patient withstood the operation well, but on the fourth postoperative day her temperature rose to 103.4° F. Procaine penicillin was supplemented at this time by 6 gm. of sulfadiazine daily, and lysis of temperature occurred over the next four days. On the fifteenth postoperative day the sulfadiazine was discontinued. The patient's temperature then gradually rose to 104.4° F. three days later, and she developed nuchal rigidity and a positive Kernig's sign. Lumbar puncture showed grossly cloudy fluid, with 2,000 white blood cells per cu. mm., 80 per cent of which were polymorphonuclears. Culture was positive for *Ps. aeruginosa*. Unfortunately, no studies of the sensitivity of this organism to the therapeutic agents were made. Re-exploration of the operative site failed to reveal a focus of infection.

Streptomycin in doses of 0.5 gm. intramuscularly every six hours was then given, and sulfadiazine was reinstituted for five days. Penicillin was increased to 4,000,000 units daily. One day later, when *Ps. aeruginosa* was reported present in the spinal fluid, aureomycin was started in a dosage of 400 mg. intravenously twice daily. During the next two days the patient was in coma, the white cell count in the spinal fluid rose to 11,500 per cu. mm., and the spinal fluid protein increased to 90 mg. per cent. She received 100 mg. of streptomycin intrathecally daily for three days, and then 50 mg. every other day for one week. The intravenous aureomycin was replaced after four days by oral doses of 1.0 gm. every six hours. On the third day of this combined therapeutic régime, the patient's temperature returned to normal and there was a remarkable improvement in her general condition. All subsequent spinal fluid cultures were negative. Spinal fluid cell counts dropped rapidly to 132 white blood cells, and the protein fell to 36 mg. per cent on the last day of intrathecal therapy. All chemotherapy was stopped 14 days after the onset of her meningitis. Although previously the patient's diabetes had been controlled on diet alone, during the period of coma and high fever it became intensified and required an average of 75 units of standard insulin daily. On intravenous fluid therapy her potassium fell to 1.8 mEq.

and her sodium to 130 mEq. per liter. Her CO_2 rose to 81 vol. per cent. Her chloride fell to 394 mg. per cent. With control of her infection and with cautious administration of parenteral potassium and chloride, this hypochloremic alkalosis cleared.

She has now been afebrile and well for two months without chemotherapy.

Discussion

Meningitis due to *Ps. aeruginosa* is a rarity. In a report by Evans [1] in 1936, 40 cases were reviewed and three new cases added. The subject was further summarized by Stanley [2] in 1947. This author discusses 41 cases which he characterized as primary *Ps. aeruginosa* meningitis. In all of these cases the portal of entry was directly into the subarachnoid space via a spinal needle, or craniocerebral trauma. He grouped 21 cases as secondary *Ps. aeruginosa* meningitis following infections of the middle ear, uterine cavity, urinary tract, lung and generalized sepsis. There was a 55 per cent mortality in the primary group, whereas the secondary group, in which the present case falls, had more than an 86 per cent mortality rate. The reason for this difference is probably the absence of a localized focus, which would continue as a source of infection in the primary group. Some of these patients received sulfadiazine and streptomycin. To quote Stanley: "The treatment has been generally unavailing, although recently sulfonamides and streptomycin have been used. . . ." This is attributed to the variability of the sensitivity of *Ps. aeruginosa* and the rapid development of resistance to streptomycin.

Until the development of streptomycin, nontoxic therapeutic agents were not available for the treatment of generalized *Ps. aeruginosa* infections.[3] Keefer [4] discusses the cure of six of a total of 11 cases of *Ps. aeruginosa* meningitis, all of whom were treated with streptomycin for two weeks with associated intrathecal therapy. "In the cases treated by streptomycin the . . . 55 per cent fatality rate reported by Stanley after repeated spinal drainage and sulfonamides . . . has been only slightly reduced."

Because the outlook for aeruginosa meningitis treated with streptomycin was still quite serious, it was felt that the patient might respond more favorably to a combination of streptomycin and aureomycin. There is experimental evidence to favor this view. Alexander,[5] in a comparative study of the effects of streptomycin, aureomycin and chloromycetin on *Ps. aeruginosa*, found that aureomycin was equivalent or slightly superior to streptomycin. She also found that among the streptomycin resistant mutants (resistant to more than 100 mcg. per c.c.), aureomycin was therapeutically effective in concentrations of from 3 to less than 25 mcg. per. c.c. She then postulated that the combined use of streptomycin and aureomycin would be the most effective therapy for *Ps. aeruginosa*. Long [6] also emphasizes the importance of the simultaneous use of antimicrobial agents of this type.

It is suggested that the response of this patient may have been aided greatly by the combined streptomycin and aureomycin therapy, inasmuch as only 14 per cent of similar cases recovered prior to 1947.

Early in this patient's course because of her comatose condition, it was considered advisable to use the newly available intravenous preparation of aureomycin. Brickhouse [7] demonstrated that the rise in serum level and cerebrospinal

fluid level is more rapid following intravenous aureomycin than with the orally administered drug. This factor may have been important during the critical phase of her illness.

SUMMARY

A case of *Ps. aeruginosa* meningitis developing subsequent to radical otic surgery is presented because of recovery associated with a combination of streptomycin and aureomycin therapy.

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CASE REPORT OF STENOSIS OF THE VENA CAVA WITH VENA CAVAL AND HEPATIC VEIN THROMBOSIS RELATED TO TRAUMA*

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APPROXIMATELY 115 cases of the Budd-Chiari syndrome have been reported to date. The most common causes of hepatic vein thrombosis are intraabdominal malignant disease, inflammatory disease and blood dyscrasias.[1-14] Trauma is thought by some to be a rare cause. Stenosis of the inferior vena cava is not a common associated finding. In 1906, Sternberg reported a case of stenosis of the inferior vena cava at the level of its hepatic portion with thrombosis of the hepatic vein.[8] Nishihowa in 1918 reported three cases with stenosis of the cava as it passed through the diaphragm, and two cases of stenosis below the opening of the hepatic vein, producing the Budd-Chiari syndrome.[8] The following case of hepatic vein thrombosis due to stenosis of the inferior vena cava at the level of

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the diaphragm is presented because of the rarity of the syndrome and the probability that trauma to the chest was directly responsible for its genesis.

Case Report

A 57 year old white male vegetable peddler was admitted to the hospital December 19, 1947, with the chief complaint of swelling of the feet, legs and abdomen of five months' duration. He had been in good health until he was hit by a truck on May 15, 1947. He was pushing a cart which was struck by the truck, and the handle of the cart was driven against his right chest. He was knocked about 50 feet and was unconscious for approximately one hour. He was admitted to a local hospital, where x-ray studies showed comminuted fractures of the right fifth and sixth ribs anteriorly and fluid in the right pleural cavity. The chest was aspirated, and 800 c.c. of blood

Fig. 1. Infrared photograph of abdomen showing dilated collateral veins.

were withdrawn. Two subsequent aspirations yielded 200 c.c. of bloody serous fluid on each occasion. Intercostal nerve block was done, and the pain was relieved. The patient was discharged after two weeks of hospitalization. No transfusions or plasma were given. Shortly after discharge he noticed some swelling of the feet and ankles, soon followed by swelling of the abdomen. One morning he noted slight swelling of the face and eyelids, which disappeared within a few hours and did not recur. The swelling of the legs and abdomen was progressive, and the legs became so edematous that he could walk only a short distance. He had no dyspnea or orthopnea. There was no cough, hemoptysis or chest pain. He denied any previous serious illness, venereal disease or alcoholism.

Physical Examination: The patient was a white male, appearing chronically ill and undernourished. Temperature, 98; pulse, 80; respirations, 20; weight, 157 pounds; height, 70 inches. There was an emaciated appearance to the upper half of

the body and edema of the subcutaneous tissues from the costal margins downward. The facies was cadaverous in appearance. There was no distention of the neck veins. There was an increased convexity of the right fifth and sixth ribs anteriorly in the anterior axillary line, with callous formation. The diaphragm moved one inch by percussion bilaterally. There were moist râles in the right lung base posteriorly.

TABLE I

Laboratory Findings on Admission and During the Terminal Six Days of Coma
Blood Chemistry, Fluid Intake and Output

	Admission	39th Hosp. Day	40th Hosp. Day	41st Hosp. Day	42nd Hosp. Day	43rd Hosp. Day	44th Hosp. Day	45th Hosp. Day
Bromsulphalein 5 mg./kg. 45 min. % retained		20	52	70				
Cephalin cholesterol flocculation	2+ 48 hr.			4+ 12 hr.				
Urea nitrogen, mg. %	15	22				65		
Blood glucose, mg. %	114			10	81 (I. V. Glucose)		97 (I. V. Glucose)	
Blood cholesterol, mg. %			85					
CO_2 combining power, mEq.			17	8		15	20	
Plasma proteins, gm.	Albumin 4.7 Globulin 2.0		Albumin 3.3 Globulin 5.3					Died
Thymol turbidity, units	5.2			8				
Blood NaCl, mg. %			630			580		
Icteric index			18	19				
Prothrombin time, % normal				5				
Van den Bergh, total, mg.	.08							
Fluid intake		Not Recorded	2,000	2,250	3,000	3,000	3,100	
Urine output			300	0	600	1,000	1,100	

Blood pressure was 104/74 mm. of Hg in the left arm and 100/78 mm. of Hg in the right arm. There were no cardiac enlargement, murmurs or arrhythmias. The abdomen was distended, and shifting dullness with a fluid wave was elicited. There were numerous tortuous veins over the abdominal wall and flanks, extending from the inguinal region onto the chest; in these veins the flow was upward (figure 1).

Because of ascites, the spleen and liver were not palpable. The genitalia were normal. There was pitting edema of the feet, legs, sacrum, abdominal wall and lower thoracic wall. Neurologic examination revealed no abnormal findings.

Laboratory Examinations: Initial urinalysis showed specific gravity 1.024; albumin, negative; sugar, negative; an occasional hyaline cast and 3 to 5 leukocytes per high power field. The erythrocyte count was 4,400,000 per cu. mm. and 12.6 gm. hemoglobin. The leukocyte count was 4,600 per cu. ml.; differential: 62 per cent polymorphonuclears, 35 per cent lymphocytes, 2 per cent eosinophils, 1 per cent basophils. A Kahn test of blood was negative. X-ray of the chest revealed the heart to be normal in size, with some elongation and tortuosity of the aorta. The left diaphragm was elevated to the level of the fourth rib anteriorly, and there were adhesions between the lateral dome of the left diaphragm and the thoracic wall. Fluoroscopic examination of the chest revealed the left diaphragm to be high. A normal excursion of both portions of the diaphragm was present. A scout film of the abdomen showed an enlarged liver, with the right lobe extending almost to the crest of the ilium. Radiologic study of the upper gastrointestinal tract was within normal limits. An electrocardiogram was within normal limits. (See table 1 for blood chemical tests.)

Course in Hospital: The patient was afebrile during the hospital stay until the last week of illness, at which time he exhibited a low grade fever with a daily maximum of 99.8° F. Venous pressure in the left antecubital vein was 125 mm. and in the left femoral vein 300 mm. of water. Circulation time (arm to tongue) was 16 seconds. After two injections of Mercuhydrin, the patient lost 13 pounds and became free of ascites and edema. At this time the liver could be easily palpated two fingerbreadths below the right costal margin in the midclavicular line. It was firm and nontender, and its edge was sharp. No nodules were felt. The spleen was not palpable at any time. After losing the edema and ascites, the patient was comfortable and was ambulatory. Three urinalyses after loss of the edema showed a persistent 1 plus albumin. On the fifteenth hospital day he began coughing up bright red blood and continued to do so intermittently for six days. These hemoptyses were not profuse, and averaged approximately 2 to 3 ounces of blood daily. During this interval, moist râles were heard over the right chest anteriorly from the third intercostal space down to the base. Repeat chest x-ray studies, including laterals, showed no change from previous studies. Sputum studies were negative for acid-fast bacilli. There was no significant increase in pulse rate. Because of continuation of the bleeding, bronchoscopy and esophagoscopy were carried out on the nineteenth hospital day. Blood was seen coming from the right main stem bronchus. The left main stem bronchus and its orifices appeared normal. No esophageal varices or areas of ulceration were seen. The cardia of the stomach was visualized and appeared normal. Three days later the leg edema and ascites began to recur, and on the thirty-third hospital day he was given Mercuhydrin; a five pound weight loss resulted. The day following he complained of nausea, vomiting and upper abdominal cramps, which persisted for two days. Following this episode the liver was slightly larger and somewhat tender, and the leg edema and ascites persisted. On the thirty-seventh hospital day he again complained of upper abdominal pain and nausea. The edema and ascites had increased slightly. On the following day an abdominal paracentesis was done, with removal of 4,000 c.c. of straw colored fluid having a specific gravity of 1.017 and 2.17 gm. of protein per 100 c.c. The cell count revealed 850 erythrocytes, 150 neutrophils and 50 lymphocytes per cu. mm. That afternoon the patient was semistuporous, and moist râles were noted over both bases posteriorly. On the next day the patient was comatose, and remained so until his death six days later. During this period he developed numerous ecchymoses over the entire body. Five days prior to death he had a generalized convulsion, following which he developed an extensor rigidity of all muscle groups, a nonsustained bilateral ankle clonus, and a bilateral Babinski response

which persisted for two days. The leg edema and ascites increased; the size of the liver remained the same. Urinalyses during this period showed a specific gravity of 1.020 and 1.024, 1 plus albumin, 1 plus bile, and granular casts with no leucine or tyrosine crystals. Four days prior to the patient's death, the white blood count was 30,000, with 85 per cent polymorphonuclears, 10 per cent stabs and 5 per cent lymphocytes (table 1). Treatment during the period of coma consisted of 50,000 units of penicillin intramuscularly three times a day, and continuous intravenous 5 per cent and 10 per cent glucose at the rate of 20 gm. of glucose per hour. In addition, he received 50 gm. of Amigen and 9 gm. of sodium chloride daily. On the forty-fifth hospital day he died quietly.

Clinical Impression: The opinion was that the patient had an obstruction of the inferior vena cava. Several observers believed that it was related to the trauma,

FIG. 2. Autopsy specimen showing stenosis of the vena cava and thrombosis of the vena cava and hepatic veins.

and that an organized hematoma near the diaphragm may have been obstructing the inferior vena cava. Other observers thought the primary process was a hepatoma superimposed on cirrhosis of the liver. The cause of death was considered due to liver failure. The possibility of a Budd-Chiari syndrome was proposed ante mortem.

Autopsy Findings: The body was that of a well developed white male in a poor state of nutrition. There was emaciation in the upper half of the body and massive edema of the lower half. A moderate icteric tint was present in the sclerae and skin. Extensive superficial vein dilatation was present over the anterior abdominal wall and right upper thigh. There was an irregular angulation deformity of the right fifth and sixth ribs in the nipple line. The peritoneal cavity contained 500 c.c. of straw colored fluid. The liver border was 8 cm. below the xiphoid and 1 cm. below the right costal margin in the midclavicular line. The entire inferior vena cava from

origin to termination was removed by careful dissection. In the vena caval foramen of the diaphragm, there was a cicatricial stricture of the inferior vena cava involving the media and adventitia of the vessel, with puckering of the intima (figure 2). The lumen at the site of the stricture admitted a small probe and measured approximately 1 mm. in diameter. A short portion of the vena cava cephalic to the stricture was greatly dilated, measuring 3.4 cm. in circumference. The vessel was likewise dilated caudal to the stricture and measured 3.8 cm. in circumference. A partially organized thrombus was present in the lumen of the inferior vena cava from the site of the stricture to the iliac veins; the thrombus extended for a short distance into the renal veins. The hepatic veins were dilated and thrombosed as a result of extension of the thrombosis of the inferior vena cava. The portal vein was widely dilated and filled with postmortem clotted blood (figure 2). The liver weighed 1,500 gm. The capsular surface was smooth and glistening, and sinusoidal hemic congestion was visible beneath the capsular surface. Surrounding the radicles of the hepatic vein were areas of yellow discoloration extending out into the liver parenchyma approximately 4 mm. The cut surface revealed a uniformly finely granular tissue of a brownish yellow hue. The usual architecture was maintained but was exaggerated by the unusually conspicuous central veins.

Microscopic examination of sections taken through the stenotic area of the vena cava revealed an organizing thrombus below the stricture at the vena caval foramen and irregular scarring of the vessel at the site of the stenosis and for a short distance superior to it. Cephalic to the stricture, the vena cava was distorted by large vascular spaces in the muscularis, with perivascular infiltrations of large mononuclear cells and lymphocytes. This inflammatory reaction was most conspicuous at the site of the stenosis and was accompanied by considerable fibrocollagenous scarring in the subendothelial layer, together with a copious ingrowth of fibroblasts into the organizing thrombus. The vena cava distal to the point of stricture, in addition to the presence of an organizing thrombus, showed a rather abundant inflammatory reaction in the outer margin of the media. There was a slight degree of re-vascularization extending from the intima and the subintimal layer into the organizing thrombus. A section taken through the hepatic vein revealed a partially organized thrombus filling the lumen. Sections of liver revealed diffuse central necrosis, characterized by dilatation and thrombosis of the central veins, with atrophy and collapse of the liver cords. Previous hemorrhage was evidenced by the presence of hemosiderin-laden macrophages. A chronic inflammatory reaction was present in occasional central vein areas. There was a moderate chronic inflammatory reaction about the portal triad. The liver cells adjacent to the areas of necrosis were swollen in many areas and showed pyknosis of their nuclei. Subacute congestion of the spleen was reflected by marked distention of the venous sinuses with blood, and by diffuse atrophy of the white pulp. Sections of kidney revealed engorgement of the interstitial vessels. In focal areas the tubular epithelial cells were pale and granular, and showed pyknosis of their nuclei. Special stains showed the major portion of these cells to contain lipoid material. The lumina of the renal veins were partially obstructed by organizing thrombi. The intima was irregularly thickened by fibrous tissue proliferation, and the smooth muscle of the media and adventitia was surrounded by moderate diffuse chronic inflammatory reaction. A partially organized thrombus in a vein of the tunica vaginalis was seen in a section of testicle.

Discussion

The etiology of the stenosis of the inferior vena cava in this case is not clear. Such stenoses have been regarded in the past as congenital in origin. The superimposed thrombosis, however, was clinically clearly associated with the patient's

trauma. The pathologic findings are entirely compatible with this concept. This case thus represents a very unusual cause of the Budd-Chiari syndrome, and is remarkable for its rather rapid fatal course.

SUMMARY

1. A case is presented of Budd-Chiari syndrome due to traumatic thrombosis of the inferior vena cava and hepatic veins.

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EDITORIAL

THE USE OF ISONICOTINYL HYDRAZINES IN THE TREATMENT OF TUBERCULOSIS

ALTHOUGH great advances have been made in the past decade in the chemotherapy of tuberculosis, all the agents hitherto available have proved to be unsatisfactory in certain important respects. Of these streptomycin and its derivatives are by far the most effective. As is well known, these antibiotics will often arrest acute fulminant pulmonary infections as well as generalized (miliary) tuberculosis, which have been intractable to all other measures. Furthermore, the serious toxic effects of streptomycin have been markedly diminished by the current regimens utilizing occasional small doses (one gram two or three times a week), since it was found that such dosage is substantially as effective as are much larger quantities. The development of drug-resistant strains has also been greatly delayed, especially if para-aminosalicylic acid is concurrently administered.[1] There is still great need, however, for some effective alternative drug, and the announcement that isonicotinic acid hydrazide exerted a potent antituberculous activity naturally aroused general interest.

The antituberculous activity of isonicotinic acid hydrazide, which has been used in the synthesis of thiosemicarbazones, was noted independently in the laboratories of Squibb (Bernstein et al.[2]) and of Hoffman-LaRoche (Greenberg et al.[3]) in experimentally infected mice. Following intravenous injections of virulent strains which uniformly cause rapidly progressive fatal infections in controls, well tolerated doses (oral or parenteral) suppressed the infection completely. When autopsied after three weeks' treatment, neither gross nor microscopic lesions could be demonstrated, and if the dose was adequate, cultures from the lungs were sterile. In a large percentage of cases, the mice remained well during a subsequent period of observation of three weeks after treatment was stopped, a feat which had not been accomplished by any drug previously used.[4] Even if treatment was postponed to the fourteenth day, when the mice were critically ill, most of them recovered.

Infections in guinea pigs and rabbits were also suppressed, although infections progressed to their usual fatal termination after treatment was stopped. Steenken et al.[5] describe the effect in guinea pigs as "dramatic,"

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superior to that of any other agent except streptomycin, and they reported that a strongly positive tuberculin reaction in these animals became negative after 30 days' treatment.

The preparations which have been most used are isonicotinic acid hydrazide (furnished by LaRoche as Rimifon and by Squibb as Nydrazid) and its isopropyl derivative (Marsilid of LaRoche). Both the effective and the toxic doses of Marsilid are somewhat greater than those of Rimifon, but otherwise there appears to be no significant difference in their effects.

In cultures in a synthetic fluid medium, growth of virulent strains of tubercle bacilli was inhibited for 14 days by concentrations of 0.025 to 0.05 γ (micrograms) per ml. of Rimifon or by 1.6 to 3.1 γ of Marsilid (about double these concentrations were required in the presence of serum). In concentrations of 10 γ per ml. it exerted a bactericidal action, as colonies on subculture diminished from 200,000 to less than 10 per ml. after five days. After five weeks' incubation, however, a growth appeared in concentrations up to 25 γ per ml., indicating the presence or development of drug-resistant organisms.[5] No inhibitory effect on other classes of microörganisms has been observed.

The toxicity of these drugs in animal experiments is relatively low. The LD_{50} dose in mice was about 144 mg. per Kg., in dogs about 50 mg. per Kg.[6, 7] Such doses after a half hour interval caused excitement, convulsions, prostration and death from respiratory failure. Somewhat smaller daily doses in dogs caused anorexia, loss of weight, tremor, ataxia, occasional convulsions, jaundice with fatty degeneration of the liver and hematuria. The maximum tolerated dose (dogs) was about 10 mg. per Kg. per day, suggesting that 4 to 5 mg. per Kg. per day would be a maximum safe human dose.[6] Larger doses (10 to 15 mg.), however, apparently can be tolerated, at least for limited periods. In longer term experiments in animals pathologic changes have been noted in the liver, spleen, kidneys and bone marrow, emphasizing the need for careful observation of human cases while under treatment.

The drugs are readily absorbed after oral administration. After a dose of 3 mg. per Kg. in man, a concentration of 1 to 3 γ per ml. may appear in the blood, 20 to 80 times the inhibitory dose in vitro.[8] Approximately the same concentration has been reported in the cerebrospinal fluid, substantially smaller amounts in pleural fluid. The drugs are excreted in the urine, and the concentration in the blood falls to about a third after 16 hours.[8]

Published reports of the effect of these drugs in human tuberculosis are still meager and cover relatively short periods of observation (4 to 15 weeks). The experience at the Sea View Hospital has been reported by Robitzek

[6] Rubin, B., et al.: Pharmacology of isonicotinic acid hydrazide (Nydrazid), Am. Rev. Tuberc. 65: 392–401, 1952.

[7] Benson, W. M., et al.: Pharmacologic and toxicologic observations on hydrazine derivatives of isonicotinic acid (Rimifon, Marsilid), Am. Rev. Tuberc. 65: 376–391, 1952.

[8] Elmendorf, D. F., Jr., et al.: The absorption, excretion, and short-term toxicity of isonicotinic acid hydrazide (Nydrazid) in man, Am. Rev. Tuberc. 65: 429–442, 1952.

et al.[9, 10] and more fully by Selikoff and Robitzek.[11] The study at the New York Hospital, Cornell Medical Service, has been reported by Elmendorf et al.[8] and more recently by McDermott et al.[12] The doses employed were usually from 2 to 4 mg. per Kg. per day (in one series, 10 mg.). Untoward symptoms were slight on the smaller doses, somewhat more disturbing on the larger, but, as described, rarely if ever serious.[11] "Vertigo" or dizziness was common and occasionally troublesome on larger doses. It was attributed to vasomotor disturbances, was not associated with an increase in blood pressure, and tended to disappear after four or five weeks. Gastrointestinal symptoms were trivial or absent except for constipation which was often troublesome and sometimes severe. Exaggeration of the deep reflexes was common, and many complained of weakness or twitchings of the leg muscles, particularly at night. There was some tendency to mental stimulation and euphoria, and a psychotic reaction appeared in one subject on large doses. Retention of urine occasionally occurred. These symptoms were attributed largely to stimulation of the central and sympathetic nervous systems. During the period of observation neither allergic reactions, cutaneous eruptions, significant hematologic disturbances, nor evidence of hepatic or renal injury appeared. The possibility of such injuries following protracted treatment, however, has not been excluded.

Elmendorf et al.,[8] on the other hand, observed no evidence of toxic injury in their series, no vertigo or manifestation of overstimulation of the nervous system.

Patients under treatment may show unaccountable and violent reactions to other drugs casually administered, particularly to those of the ephedrine and atropine groups, and also, it is said, to Demerol (unpublished report). Great caution should be observed in this regard.

The patients reported from the Sea View Hospital comprised 92 cases of extensive bilateral pulmonary tuberculosis under treatment for from four to 15 weeks.[11] All showed cavitary caseous-pneumonic pulmonary tuberculosis in roentgenograms, with tubercle bacilli in the sputum, usually in very large numbers. Sixty-nine were classed as far advanced, 23 as moderately advanced. The prognosis was regarded as "uniformly poor." Streptomycin had been administered unsuccessfully to 76, usually with para-aminosalicylic acid, and in more than half, artificial pneumothorax or other surgical procedures had been tried. Forty-six were classed as "progressive,"

[9] Robitzek, E. H., et al.: Chemotherapy of human tuberculosis with hydrazine derivatives of isonicotinic acid. Preliminary report of representative cases, Quart. Bull. Sea View Hosp. **13**: 27–51, 1952.

[10] Robitzek, E. H. et al.: Hydrazine derivatives of isonicotinic acid (Rimifon, Marsilid) in the treatment of acute progressive caseous-pneumonic tuberculosis, Am. Rev. Tuberc. **65**: 402–428, 1952.

[11] Selikoff, I. J., and Robitzek, E. H.: Tuberculous chemotherapy with hydrazine derivatives of isonicotinic acid, Dis. Chest **21**: 385–438, 1952.

[12] McDermott, W. et al.: Isonicotinic acid hydrazide in the treatment of tuberculosis in man, Reported at the sixty-fifth annual meeting of the Association of American Physicians, Atlantic City, N. J., May 6, 1952.

with fever, anorexia, loss of weight, weakness, signs of "toxicity," cough and usually abundant sputum. Many were bedfast. The balance were more chronic in type, and relatively "stationary."

According to the authors every patient was benefited by the treatment. The most striking feature was early relief from the systemic symptoms of the infection. There was relief from the malaise and apathy, with return of appetite which was described as becoming ravenous in many cases, and rapid gain in weight (average of 18 pounds in nine weeks for the whole group). The temperature usually fell to normal by lysis within one to two weeks (rarely longer), occasionally abruptly within one to three days. Every case was said to be afebrile at the time of the report. The cough and volume of the sputum either were diminished or eliminated "in every case," often within a few days, regularly by the end of the second week. In 25 per cent the sputum became negative (in stained films from concentrated sputum or gastric washings; culture reports were not available). No case is mentioned in which a clinical relapse occurred, suggesting that drug-resistance had developed. No information regarding tests of susceptibility of the cultures isolated was available at the time of the report.

Changes in roentgenograms were not demonstrable in 42 cases. In two cases cavities "closed"; and in 26 cases they appeared smaller. In many the areas of exudate diminished in size, although there was some extension in four. In view of the nature and extent of the initial lesions and the short period of observation, extensive clearing could hardly be anticipated.

Little has been reported by this group regarding other types of the disease. Clinical improvement was noted in 10 cases of associated laryngeal tuberculosis, in cases of glossitis and otitis, and in several cases of osseous tuberculosis.

Reports of the study at the New York Hospital are still scanty. Clinically the patients showed substantial improvement, with increased appetite, gain in weight and reduction in fever, but defervescence did not occur with uniformity.[8] McDermott [12] reported treatment of several cases of acute miliary tuberculosis, with notable improvement and apparent arrest in five cases without meningeal involvement. Those with associated meningitis did less well. Of 12 cases of tuberculous meningitis, six died early in the course, and six showed some clinical improvement. Of 38 cases of pulmonary tuberculosis, none spread while under treatment and most of them improved. This, however, appears to have been more gradual and less spectacular than was the improvement described at the Sea View Hospital. These observers stated [8] that at the time it was "not possible to make any positive statements concerning the effectiveness of this compound in the treatment of tuberculosis in humans."

The glowing reports from the Sea View Hospital regarding the uniformity, the promptness and the astonishing extent of the improvement observed in these otherwise hopeless cases seem too good to be true. Even

if reasonable allowance is made for a natural enthusiasm and full duplication proves impossible, the short-term results appear to equal if not surpass those obtained with streptomycin. In view of the much greater restraint shown by the New York Hospital group, it would seem rash to draw any far reaching conclusions until adequate confirmation is obtained from other clinics.

A possible partial explanation for these somewhat divergent results might be found in the status of the bacterial population. There is evidence that in cultures the antibiotic effect is exerted primarily upon organisms which are multiplying rapidly, and much less upon old relatively static cultures. The same may be true in vivo. Organisms multiplying rapidly in an acute fulminant case might be more profoundly affected than those in a patient with a more chronic type of the disease in which the organisms are relatively quiescent.

The crucial point in determining the ultimate value of these drugs is the question of drug-resistance. It is already known that resistance can be developed in laboratory cultures, although apparently less easily and less explosively than to streptomycin. Drug-resistant individuals have been isolated from large populations of drug-sensitive cultures which have not been exposed to these drugs. More significant is the recent brief note of Steenken et al.[18] They tested serial cultures from six patients with chronic cavitary pulmonary lesions while under treatment, and in three cases after seven weeks "definite evidence of increased bacillary resistance was noted." In one, this was apparent after 26 days. This was followed by a bacteriological relapse in each.

Such observations make it certain that drug-resistance will be a serious practical problem, however potent the initial effect of the drugs may be. Valid conclusions are impossible until it is known how frequently and how early resistance is likely to develop and particularly how it can be prevented. Pending more information, these drugs are not suitable for promiscuous use. At the worst, however, they should prove valuable in securing an arrest in the more fulminant types of infection, as was streptomycin before the recent, more effective methods of administration had been perfected.

P. W. C.

[18] Steenken, W., Jr., et al.: Drug resistant tubercle bacilli from patients treated with isonicotinic acid hydrazides, J. A. M. A. **149**: 187, 1952 (May 10, correspondence).

REVIEWS

Accelerated Conduction: The Wolff-Parkinson-White Syndrome and Related Conditions. By MYRON PRINZMETAL, M.D., REXFORD KENNAMER, M.D., JOSHUA FIELDS, M.D., ELIOT CORDAY, M.D., JOHN A. OSBORNE, M.D., and L. ALLEN SMITH, M.D. 110 pages; 14 × 22.5 cm. Grune and Stratton, New York. 1952. Price, $4.00.

In this monograph, the authors present and interpret the results of a series of experimental investigations of the Wolff-Parkinson-White syndrome (paroxysmal tachycardia in association with an electrocardiographic pattern consisting of a short PR interval, usually less than 0.10 second in duration, and a prolonged QRS complex slurred on the upstroke). Simultaneous high speed photographs and electrocardiographic tracings were utilized in an effort to correlate the intimate details of the disturbed motion which occurs during WPW aberration. WPW complexes were produced by stimulating the ventricles or A-V node by a variety of technics. They conclude that, ". . . the fundamental disorder appears to consist of a failure of a part of the A-V node to delay the auricular impulse for the normal period of time before allowing its passage to the ventricle . . ." and suggest that the term "accelerated conduction" be employed to designate this condition. They further distinguish a nodal from a ventricular type and conclude that ". . . the WPW complex as a whole is thus seen to be a fusion complex composed of a premature localized contraction in one ventricle and the normal contraction of the rest of the ventricular musculature."

There have been many approaches to the problems of the WPW syndrome, utilizing analyses of clinical material, experimental animals, intracardiac and esophageal electrocardiography, and vectorcardiography. Many workers accept the explanation of a functioning accessory anatomical pathway by means of which the auricular impulse reaches the ventricles, rather than the concept of accelerated conduction in the A-V node as advanced by Prinzmetal and his group. The conclusions reached in this monograph are certainly suggestive, but by no means final. The elaborate high speed cinematography of ventricular motion in "WPW aberrations" was carried out when the ventricle was stimulated by applying direct current to the epicardial or endocardial surface of the ventricle. It must follow that the description of a "usual WPW beat" is actually that of an induced ventricular contraction. Whether or not a similar mechanism is present in WPW remains conjectural.

The ventricular complexes referred to throughout this study as WPW complexes all too often lack the characteristic slur or delta wave at the beginning of the QRS complex. This slurred deflection has been referred to by others as the so-called anomalous component and is regarded by them as an important part of the WPW ventricular complex. The beats produced experimentally by Prinzmetal and his group are probably fusion beats, as the authors suggest; but such fusion beats are not necessarily the same as those seen in WPW because of superficial electrocardiographic similarities.

The technics employed in this investigation are commendable, and the results are challenging and suggestive. However, they should be regarded as extremely tentative and requiring further elaboration before they can be accepted as more than highly theoretical formulations.

L. S.

Modern Electrocardiography. Volume 1: *The P-Q-R-S-T-U Complex.* By EUGENE LEPESCHKIN, M.D., University of Vermont College of Medicine; foreword by FRANK N. WILSON, M.D., University of Michigan Medical School. 598 pages; 18 × 26 cm. The Williams and Wilkins Company, Baltimore, Maryland. 1951. Price, $12.00.

The author states that ". . . the purpose of this book is to give a comprehensive but concise summary of the progress of electrocardiography since 1933. . . ." Only the form of the electrocardiogram in the regularly beating heart is discussed in the present volume since a second volume to appear at a later date will include disturbances of cardiac rhythm. Included is a summary of the complete electrocardiographic literature. There is an excellent bibliography of approximately 9,000 references and an extensive system of cross-references. There are chapters on electrocardiographic artefacts; leads; electrical activity of heart muscle; electrocardiograms of animals; influence of physiologic factors; physical agents; chemicals; vitamins; hormones; and chapters on various pathologic entities.

Unfortunately there is a paucity of adequate illustrative electrocardiograms which would have helped clarify many descriptive passages. The large mass of material is presented in an uncritical manner with no real attempt at proper emphasis or orientation. This volume will probably find its best use, as the author suggests, as a supplementary volume when used with existing textbooks on electrocardiography.

It is recommended as a source for reference material to those specifically interested in electrocardiography. Here, one may quickly find in one volume a comprehensive, albeit uncritical, review of the electrocardiographic literature.

L. S.

The Practice of Endocrinology. 2nd Ed. Edited by RAYMOND GREENE, M.A., D.M., M.R.C.P. 389 pages; 25 × 16 cm. Eyre & Spottswoode, Great Britain; Agents for U.S.A.: J. B. Lippincott Company, Philadelphia. 1951. Price, $12.50.

A second edition brings nearer to date this British text on endocrinology. Its purpose is given in its Preface: "The reputation of endocrinology as a special branch of medicine has suffered much in past years, not only from the dubious products of a few commercial houses but also from the ignorance of the basic facts of the science displayed by a large proportion of practising physicians. It is in the hope of helping the general practitioner to display in his treatment of endocrine disorder the high standard he has achieved in other branches of his profession that this book has been planned." As a general survey of general endocrinology it is useful. With emphasis rather on treatment, one or several remedial measures are proposed for each condition discussed, usually with a glimpse of rationale behind them, but occasionally empiricism wins—as in discussing pubescent bleeding on page 179: "(e) Thyroid extract is often highly effective." Therapy is covered more broadly than in most texts, and can give food for thoughtful trial in some cases, resistant perhaps to one's usual maneuvers.

The format is generally good, though the "fine" print could be finer to be more readily recognized as such. There are the usual divisions into the major endocrinologic branches with a small bibliography at the end of each section and a useful index. The illustrations and charts are good. One colored plate of Addisonian pigmentation is striking. The American reader will be interested in the transatlantic phraseology (corpulence for obesity, slimming for reducing, etc.) and spellings (stuporose) that add a spice to the somewhat repetitious text.

A good feature is the focus on the hypothalamus as the highest echelon of the endocrine system, a concept often forgot by American organ-ists. With emphasis on treatment, descriptions and explanations of disorders are usually kept from getting too involved. Time is taken to define terms commonly misapplied.

Among the poorer features is a tendency to authoritarianism, to say "is not known" where "is not agreed upon" were truer. Perhaps vaginal temperatures are used for fertility curves in England, but rectal readings are more used here. The emphasis on 17-ketosteroid levels and perirenal air insufflation in adrenal disorders would take them out of the general practitioner range in this country.

Neither a text for expert nor for beginner, this book may find usefulness among that middle group of physicians who have practical therapeutic sense and can realize with the author that "endocrinology is probably the fastest growing-point in medicine to-day and any book is bound to grow out of date between manuscript and proof."

C. A.

Manic-Depressive Psychosis and Allied Conditions. By LEOPOLD BELLAK, M.D.; with BLAISE PASQUARELLI, M.D., ERNEST PARKES, and SONYA SOREL BELLAK, and the collaboration of SYDELL BRAVERMAN, M.D.; foreword by WINFRED OVERHOLSER, M.D. 306 pages; 23.5 × 15.5 cm. Grune & Stratton, Inc., New York. 1952. Price, $9.75.

The literature on psychiatric research is so voluminous at present that it seems impossible for the busy doctor to be well informed. It is to Dr. Bellak and his co-workers' great credit that they have collected and condensed in one volume the world literature pertaining to manic-depressive psychosis. The material is presented in a clear, comprehensive manner and organized according to causation, diagnosis, treatment, and prevention. The major forms of treatment are described in detail. The reader will find about 1,200 references. Very interesting is the author's own theory of a multiple factor psychosomatic causation of manic-depressive psychosis. In addition the volume contains material about some allied conditions such as psychiatric reactions to pregnancy, involutional psychoses, depressions of old age.

There is no doubt that this book will be greatly welcomed by clinical as well as practicing psychiatrists. It will be of special value to doctors interested in research.

H. W. N.

Good Foods for Diabetics. By ELEANOR RECORD SIGEL. 144 pages; 13.5 × 20 cm. Harper & Brothers, New York. 1951. Price, $2.50.

It is very difficult to evaluate the usefulness of this little book. Part of it consists of suggestions for foods suitable for breakfast, lunch and dinner menus without, however, helping very much toward the adjustment of a quantitative diet.

The greater part of the book is made up of a number of favorite recipes that the author has been using for many years. They are no doubt delicious, but it is also true that very little attempt is made to suggest quantitative measurements. A startling chapter is entitled "Desserts for the Rest of the Family—Beverages." These recipes are obviously productive of very pleasant confections, but since they are all of the high carbohydrate and grossly sweet varieties, the reviewer feels that some diabetic patients might believe that this gives them permission to go ahead with foods of this character.

T. N. C.

Chlorosis: A Retrospective Investigation. Monograph which appeared as a supplementary volume of "Acta Medica Belgica." By EMIL SCHWARTZ. From the Harry W. Sherman Hematology Research Laboratories, and the Clinical Service of Dr. Raphael Isaacs, Attending Physician in Hematology, Michael Reese Hospital, Chicago, U. S. A. 1951. 199 pages; 16 × 24.5 cm. (paper-bound). Price, Belgian francs 180.

This supplement, as the author states, is devoted to a retrospective investigation of chlorosis and consists of a critical evaluation of the concepts held regarding etiology

and pathogenesis viewed in the light of modern knowledge in such fields as endocrinology, nutrition, metabolism and genetics and in the social trends of fashion.

In this volume of 199 pages, one small chapter of nine pages is devoted to the clinical picture of the disease while the remainder views the problems of etiology and pathogenesis through a mist of statistics and references to the literature, some 438 of which are listed in the bibliography and from which it is difficult to form any clear cut picture of the mechanisms of the disease.

To the present generation in the field of medicine chlorosis is of purely historical importance. While the volume may prove of considerable value to the medical historian and statistician, its contribution toward the stimulation of interest in the more general reader will be small.

R. A. N.

Alcoholism, Report on the First Session of the Alcoholism Subcommittee, WHO Expert Committee on Mental Health, World Health Organization Technical Report Series No. 42, Geneva, December 11–16, 1950. 24 pages; 16 × 24 cm. (paperbound). World Health Organization, Geneva; Agent in U.S.A.: Columbia University Press, International Documents Service, 2960 Broadway, New York 27. 1951. Price, 15¢.

This brief report is in no way a complete or final study. However, although it is a preliminary "first report," it adheres to the high standards set by other Technical Reports of WHO. It describes the problem clearly and thoughtfully, recommends specific further steps and studies that would help, and discusses various treatment methods that have proved most promising. The report stresses the fact that alcoholism is primarily a medical problem and requires medical methods for its study as well as treatment. Physicians who wish to clarify and bring up to date their ideas regarding this baffling problem should acquire this report.

H. W. N.

BOOKS RECEIVED

Books received during May are acknowledged in the following section. As far as practicable those of special interest will be selected for review later, but it is not possible to discuss all of them.

Accelerated Conduction: The Wolff-Parkinson-White Syndrome and Related Conditions (Modern Medical Monographs). By MYRON PRINZMETAL, M.D., REXFORD KENNAMER, M.D., ELIOT CORDAY, M.D., JOHN A. OSBORNE, M.D., JOSHUA FIELDS, M.D., and L. ALLEN SMITH, M.D. 110 pages; 22.5 × 14 cm. 1952. Grune & Stratton, New York. Price, $4.00.

The Biology of Mental Health and Disease: The Twenty-seventh Annual Conference of the Milbank Memorial Fund. With 108 Contributors; Foreword by STANLEY COBB, M.D. 654 pages; 24.5 × 16 cm. 1952. Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, New York. Price, $10.00.

Clinical Ballistocardiography. By HERBERT R. BROWN, JR., M.D., VINCENT DELALLA, JR., M.D., MARVIN A. EPSTEIN, M.D., and MARVIN J. HOFFMAN, M.D. 188 pages; 22 × 14.5 cm. 1952. The Macmillan Company, New York. Price, $5.50.

Differentialdiagnose innerer Krankheiten. By DR. ROBERT HEGGLIN. 454 pages; 24.5 × 17.5 cm. 1952. Georg Thieme Verlag, Stuttgart; Agents for U. S. A.: Grune & Stratton, New York. Price, Ganzleinen DM 49.80.

Endocrine Diagnosis. By H. Ucko, M.D. 513 pages; 22 × 14.5 cm. 1951. Staples Press, Inc., New York. Price, $8.50.

Essentials in Diseases of the Chest for Students and Practitioners. By Philip Ellman, M.D., F.R.C.P., Consultant Physician in Diseases of the Chest to the North-East Metropolitan Regional Hospital Board at East Ham Chest Clinic, Harts Sanatorium and Plaistow Hospital Chest Unit, London, etc.; with a Foreword by Sir Robert A. Young, C.B.E., M.D., F.R.C.P., Hon. Consultant Physician to the Middlesex Hospital and to the Brompton Hospital, etc. 400 pages; 23 × 14 cm. 1952. Oxford University Press, New York. Price, $6.50.

Expert Committee on Cholera: First Report—World Health Organization Technical Report Series No. 52. 18 pages; 24 × 16 cm. (paper-bound). 1952. World Health Organization, Geneva; Agents in U. S. A.: Columbia University Press, International Documents Service, New York. Price, 15 cents.

Expert Committee on Drugs Liable to Produce Addiction: Third Report—World Health Organization Technical Report Series No. 57. 14 pages; 24 × 16 cm. (paper-bound). 1952. World Health Organization, Geneva; Agents in the U. S. A.: Columbia University Press, International Documents Service, New York. Price, 10 cents.

Expert Committee on the International Pharmacopoeia: Ninth Report—World Health Organization Technical Report Series No. 50. 33 pages; 24 × 16 cm. (paper-bound). 1952. World Health Organization, Geneva; Agents in U. S. A.: Columbia University Press, International Documents Service, New York. Price, 25 cents.

The Fight Against Tuberculosis: An Autobiography. By Francis Marion Pottenger, M.D. 276 pages; 22 × 14.5 cm. 1952. Henry Schuman, New York. Price, $4.00.

Für und wider die Sterilisierung aus Eugenischer Indikation. By Dr. Hans Nachtsheim. 64 pages; 21 × 15 cm. (paper-bound). 1952. Georg Thieme Verlag, Stuttgart; Agents for U. S. A.: Grune & Stratton, Inc., New York. Price, Kart. DM 5.70.

Functional Endocrinology from Birth Through Adolescence. By Nathan B. Talbot, M.D., Associate Professor of Pediatrics, Harvard University, etc.; Edna H. Sobel, M.D., Formerly Research Fellow in Pediatrics, Harvard University; at present Instructor in Pediatrics, University of Cincinnati College of Medicine, etc.; Janet W. McArthur, M.D., Instructor in Gynecology, Harvard University, etc.; and John D. Crawford, M.D., Instructor in Pediatrics, Harvard University, etc. 638 pages; 26 × 17.5 cm. 1952. Published for the Commonwealth Fund by Harvard University Press, Cambridge, Massachusetts. Price, $10.00.

Grundlagen und Sprache der Phthise- und Tuberkuloseforschung. By Prof. Dr. Siegfried Gräff. 61 pages; 24.5 × 17 cm. (paper-bound). 1952. Georg Thieme Verlag, Stuttgart; Agents for U. S. A.: Grune & Stratton, New York. Price, Kart. DM 6.60.

Hagerstown Health Studies: An Annotated Bibliography—Public Health Bibliography Series, No. 6. By Violet B. Turner, Consultant, Division of Public Health Methods, Public Health Service. 38 pages; 23.5 × 15 cm. (paper-bound). 1952. Federal Security Agency, Public Health Service, U. S. Government Printing Office, Superintendent of Documents, Washington, D. C. Price, 20 cents.

Hemifacial Spasm: A Clinical and Pathophysiological Study. By ROBERT WARTENBERG, M.D.; Foreword by MACDONALD CRITCHLEY, M.D. 86 pages; 22 × 14.5 cm. 1952. Oxford University Press, New York. Price, $4.00.

Injury of the Xiphoid. By MICHAEL BURMAN and SAMUEL E. SINBERG. 92 pages; 23.5 × 15.5 cm. 1952. Columbia University Press, New York. Price, $3.50.

Klinische Physiologie und Pathologie. By PROF. DR. FERDINAND HOFF. 810 pages; 24.5 × 18 cm. 1952. Georg Thieme Verlag, Stuttgart; Agents for U. S. A.: Grune & Stratton, Inc., New York. Price, Ganzleinen DM 49.50.

Lehrbuch der inneren Medizin—in 2 volumes. By M. BROGLIE, Schleswig; H. DENNIG, Stuttgart; K. HANSEN and W. GRONEMEYER, Lübeck; N. HENNING, Würzburg; A. HEYMER, Essen; H. REINWEIN, Kiel; F. SCHELLONG, Münster; G. SCHALTENBRAND, Würzburg, and H. SCHULTEN, Köln. 972 pages, Vol. I; 1,060 pages, Vol. II; 24 × 17.5 cm. 1952. Georg Thieme Verlag, Stuttgart; Agents for U. S. A.: Grune & Stratton, Inc., New York. Price, DM 41.– per volume.

Medical Biographies: The Ailments of Thirty-three Famous Persons. By PHILIP MARSHALL DALE, M.D. 259 pages; 22 × 14.5 cm. 1952. University of Oklahoma Press, Norman. Price, $4.00.

Mental Disorders: Diagnostic and Statistical Manual. Prepared by The Committee on Nomenclature and Statistics of the American Psychiatric Association. 130 pages; 23 × 15 cm. (paper-bound). 1952. American Psychiatric Association, Mental Hospital Service, Washington, D. C. Price, $1.50.

The Merck Index of Chemicals and Drugs: An Encyclopedia for the Chemist, Pharmacist, Physician, and Allied Professions. 6th Ed. 1,167 pages; 23.5 × 15.5 cm. 1952. Merck & Co., Inc., Rahway, N. J. Price, $7.50, regular edition; $8.00, thumb-index edition.

Organization and Operation of Civil Defense Casualty Services. Part III: Medical Records for Casualties—TM-11-3 (United States Civil Defense, Federal Civil Defense Administration). 31 pages; 23.5 × 14.5 cm. (paper-bound). 1952. United States Government Printing Office, Superintendent of Documents, Washington, D. C. Price, 15 cents.

Poisoning: A Guide to Clinical Diagnosis and Treatment. By W. F. VON OETTINGEN, M.D., Ph.D., National Institutes of Health, U. S. Public Health Service, Federal Security Agency, Bethesda, Md. 524 pages; 24 × 16 cm. 1952. Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, New York. Price, $10.00.

P-Q-R-S-T: A Guide to Electrocardiogram Interpretation. 3d Ed. By JOSEPH E. F. RISEMAN, M.D., Clinical Associate in Medicine, Harvard Medical School, etc. 123 pages; 14.5 × 21.5 cm. 1952. The Macmillan Company, New York. Price, $4.00.

Radiological Decontamination in Civil Defense (United States Civil Defense, Federal Civil Defense Administration, Technical Manual). 31 pages; 23.5 × 14.5 cm. (paper-bound). 1952. United States Government Printing Office, Superintendent of Documents, Washington, D. C. Price, 15 cents.

Reduce and Stay Reduced. By NORMAN JOLLIFFE, M.D., Director, Bureau of Nutrition, Department of Health, City of New York. 235 pages; 21 × 14 cm. 1952. Simon and Schuster, New York. Price, $2.95.

Spleen Puncture. By SVEN MOESCHLIN; translated by A. PINEY, M.D. 229 pages; 25 × 16 cm. 1951. Grune & Stratton, New York. Price, $5.50.

The Story of the Adaptation Syndrome (Told in the Form of Informal, Illustrated Lectures). By HANS SELYE, M.D., Ph.D. (Prague), D.Sc. (McGill), F.R.S. (Canada), Professor and Director of the Institut de Médecine et de Chirurgie expérimentales, Université de Montréal. 225 pages; 23.5 × 15.5 cm. 1952. Acta, Inc., Montreal. Price, $4.50.

Surgical Forum: Proceedings of the Forum Sessions, Thirty-seventh Clinical Congress of the American College of Surgeons, San Francisco, California, November, 1951. Surgical Forum Committee: OWEN H. WANGENSTEEN, M.D., F.A.C.S., Minneapolis, Chairman; WARREN H. COLE, M.D., F.A.C.S., Chicago; ROBERT E. GROSS, M.D., F.A.C.S., Boston; MICHAEL L. MASON, M.D., F.A.C.S., Chicago; CARL A. MOYER, M.D., F.A.C.S., Dallas; I. S. RAVDIN, M.D., F.A.C.S., Philadelphia. 667 pages; 25.5 × 16.5 cm. 1952. W. B. Saunders Company, Philadelphia. Price, $10.00.

A Textbook of Pharmacology: Principles and Application of Pharmacology to the Practice of Medicine. By WILLIAM T. SALTER, M.D., Professor of Pharmacology, Yale University School of Medicine. 1,240 pages; 26 × 18 cm. 1952. W. B. Saunders Company, Philadelphia. Price, $15.00.

The Treatment of Acute Dehydration in Infants—Medical Research Council Memorandum No. 26. By a Working Team appointed and advised by the Committee on Acute Infections in Infancy. 49 pages; 24.5 × 15 cm. (paper-bound). 1952. Her Majesty's Stationery Office, London. Price, three shillings net.

Tuberculosis of Bone and Joint. 2nd Ed. By G. R. GIRDLESTONE, Sometime Nuffield Professor of Orthopaedic Surgery in the University of Oxford; and E. W. SOMERVILLE, M.B., F.R.C.S. (Ed.), Orthopaedic Surgeon to the Wingfield-Morris Orthopaedic Hospital, Oxford. From the Nuffield Orthopaedic Centre. 314 pages; 25 × 17 cm. 1952. Oxford University Press, New York. Price, $8.75.

Überlastungs- und Aufbrauchsschäden an Herz und Kreislauf: Klinik, Prophylaxe, Therapie. Contributions by the VEREINIGUNG DER BAD NAUHEIMER ÄRZTE. 139 pages; 24.5 × 17 cm. (paper-bound). 1952. Verlag von Dr. Dietrich Steinkopff, Darmstadt. Price, DM 13.50.

Working Programs in Mental Hospitals: Proceedings of the Third Mental Hospital Institute Held Under the Auspices of the Mental Hospital Service of the American Psychiatric Association, Kentucky Hotel, Louisville, Kentucky, October 15–18, 1951. Edited by DANIEL BLAIN, M.D., Medical Director, A.P.A., with the staff of the A.P.A. Mental Hospital Service. 224 pages; 23 × 15 cm. (paper-bound). 1952. American Psychiatric Association, Mental Hospital Service, Washington, D. C. Price, $2.50.

COLLEGE NEWS NOTES

New Life Members

The College is gratified to announce that the following Fellows have become Life Members of the American College of Physicians since the publication of the last list in the May issue of this journal:

Dr. Robert O. Garvin, Pittsburgh, Pa.
Dr. Robin N. Allin, Madison, Wis.
Dr. Albert J. Erdmann, Jr., New York, N. Y.
Dr. Max S. Franklin, St. Louis, Mo.
Dr. William J. Sullivan, Bronxville, N. Y.
Dr. Morris Alan Gold, Butte, Mont.
Dr. Robert M. Woolford, Cincinnati, Ohio
Dr. Archibald C. Cohen, Butler, Pa.
Dr. Alfred H. Hill, San Antonio, Tex.
Dr. Walter Kempner, Durham, N. C.
Dr. Robert E. Scherb, Bakersfield, Calif.

Research Fellowships

The American College of Physicians announces that a limited number of Fellowships in Medicine will be available from July 1, 1953-June 30, 1954. These Fellowships are designed to provide an opportunity for research training either in the basic medical sciences or in the application of these sciences to clinical investigation. They are for the benefit of physicians who are in the early stages of their preparation for a teaching and investigative career in Internal Medicine. Assurance must be provided that the applicant will be acceptable in the laboratory or clinic of his choice and that he will be provided with the facilities necessary for the proper pursuit of his work. The stipend will be from $3,000 to $3,500.

Application forms will be supplied on request to The American College of Physicians, 4200 Pine Street, Philadelphia 4, Pa., and must be submitted in duplicate not later than October 1, 1952. Announcement of awards will be made November, 1952.

Western Michigan Regional Meeting

The spring meeting of the Western Michigan Group of the American College of Physicians was held at the Hart Hotel, Battle Creek, May 14, 1952. Forty physicians were in attendance. The meeting started at 4:30 p.m. with a presentation of three cases. There followed a short social hour and dinner, the latter being addressed by Capt. W. S. Milne, M.D., on the subject of hepatitis. His paper was based on the experience with the disease at the Percy Jones Hospital. The autumn meeting of the Western Michigan Group will be held at Muskegon during October.

Schedule of A.C.P. Postgraduate Courses, Autumn, 1952

The Committee on Postgraduate Courses of the American College of Physicians has approved the following schedule of courses for the autumn of 1952. The regis-

tration fee for each course will be $30.00 for Members and $60.00 for Non-members. The detailed Postgraduate Bulletin and registration forms are available through the American College of Physicians, 4200 Pine Street, Philadelphia 4, Pennsylvania.

	Sept.	October				November				December		
	30–Oct. 4	6–11	13–18	20–24	27–31	3–7	10–15	17–21	24–29	1–6	8–13	15–20
RECENT TRENDS IN THE DIAGNOSIS AND TREATMENT OF CARDIOVASCULAR DISEASE: Mount Sinai Hospital, New York, N. Y.; Arthur M. Master, M.D., F.A.C.P., and Charles K. Friedberg, M.D., F.A.C.P., Co-Directors.	X											
INTERNAL MEDICINE, SELECTED SUBJECTS: University of Pittsburgh School of Medicine, Pittsburgh, Pa.; Roy R. Snowden, M.D., F.A.C.P., Director.		X										
CARDIOVASCULAR DISEASE: Emory University School of Medicine, Emory University, Ga.; R. Bruce Logue, M.D., F.A.C.P., Director.				X								
INTERNAL MEDICINE: Cornell University Medical College and The New York Hospital, New York, N. Y.; David P. Barr, M.D., F.A.C.P., Director.						X			Thanksgiving Week			
SELECTED TOPICS IN HEMATOLOGY: New England Center Hospital, Boston, Mass.; William Dameshek, M.D., F.A.C.P., Director.							X					
INTERNAL MEDICINE, CORRELATION OF NEW AND EXISTING BASIC AND CLINICAL FACTORS IN DIAGNOSIS AND TREATMENT: Presbyterian Hospital and the University of Illinois College of Medicine, Chicago, Ill.; Frank B. Kelly, M.D., F.A.C.P., Director.								X				
GASTRO-ENTEROLOGY: University of Pennsylvania Graduate School of Medicine, Philadelphia, Pa.; Henry L. Bockus, M.D., F.A.C.P., Director.										X		
INTERNAL MEDICINE: University of California School of Medicine, Medical Extension, at the Franklin Hospital, San Francisco, Calif.; Stacy R. Mettier, M.D., F.A.C.P., Director; H. Clare Shepardson, M.D., F.A.C.P., Co-Director.											X	

The dates of the last two courses had not been determined at the time of the preparation of this announcement.

A.C.P. Regional Meetings

Autumn, 1952–Winter, 1953

Territory	City	Date	Governor(s)	Official Guest(s)
West Virginia	White Sulphur Springs	July 25	Paul H. Revercomb	T. Grier Miller, President
North Dakota	Grand Forks	Sept. 13	Robert B. Radl	?
Western New York	Syracuse	Oct. 3	E. C. Reifenstein	T. Grier Miller, President E. R. Loveland, Exec. Sec.
Montana–Wyoming	Great Falls	Oct. 10–11	Harold W. Gregg	?
Pacific Northwest (Ore., Wash., Idaho, Alta., B. C.)	Vancouver, B. C.	Oct. 17–18	Meri L. Margason George H. Anderson Richard P. Howard John W. Scott	T. Grier Miller, President
Arizona–New Mexico	Albuquerque	Oct. 29	Leslie R. Kober	?
New Jersey	Newark	Nov. 5	Edward C. Klein, Jr.	T. Grier Miller, President E. R. Loveland, Exec. Sec. Richard A. Kern, Sec. Gen.
Southeastern (Ala., Fla., Ga., S. C., Cuba)	Havana	Nov. 7, 8, 9	E. Dice Lineberry William C. Blake Carter Smith Robert Wilson, Jr. Jose J. Centurion	T. Grier Miller, President E. R. Borts, Regent E. R. Loveland, Exec. Sec.
Midwest (Ill., Ind., Iowa, Mich., Minn., Ohio, Wis.)	Chicago	Nov. 22	Howard Wakefield C. H. Drenckhahn J. O. Ritchey B. F. Wolverton Douglas Donald Wesley W. Spink Charles A. Doan Karver L. Puestow	T. Grier Miller, President LeRoy H. Sloan, Pres.-Elect E. R. Loveland, Exec. Sec.
North Carolina	Winston-Salem	Dec. 4	Elbert L. Persons	T. Grier Miller, President
Eastern Pennsylvania	Philadelphia	Jan. 16	Thomas M. McMillan	T. Grier Miller, President et al.
Colorado	Denver	Feb. 17	C. F. Kemper	?
Virginia	?	Feb. 26	C. M. Caravati	?
Kansas	Kansas City	March 20	William C. Menninger	?

Coming Examinations by Certifying Boards

The American Board of Pathology, William B. Wartman, M.D., Secretary-Treasurer, Northwestern University Medical School, 303 E. Chicago Ave., Chicago 11, Ill.

Examinations to be held at Northwestern University Medical School, October 9–11, 1952:

Pathologic Anatomy—Oct. 9, a.m. and p.m.; Oct. 10, a.m.
Clinical Pathology—Oct. 10, p.m.; Oct. 11, a.m. and p.m.

The American Board of Pediatrics, John McK. Mitchell, M.D., Executive Secretary, 6 Cushman Rd., Rosemont, Pa.

Oral Examination—Chicago, Ill., October 24–26, 1952.

James Edgar Paullin Scholarship Fund

In honor of the late James Edgar Paullin, M.D., M.A.C.P., Atlanta, Ga., but long preceding his death, the James E. Paullin Scholarship Fund was established for needy medical students of Emory University School of Medicine. Gifts to the fund thus far have totalled $16,878.27, with an additional $1,413.00 outstanding in pledges.

Mr. Furnie W. Johnston, Jr., of Brundidge, Ala., is the first recipient of a $500.00 grant from the Fund. He is a junior this year at Emory University, and is making fine progress toward the completion of his degree. Dr. Paullin, prior to his passing, knew of the awarding of this scholarship, and had the opportunity to meet the first recipient.

The Committee in charge of this Fund expresses the hope to be able soon to award a $1,000 scholarship each year from the investment return from the Fund, without having to go into the principal. In order to do this, the Fund must have a total of about $30,000.00 or approximately $12,000.00 more than at present. Some persons are making pledges of annual donations to this Fund extending over a period of several years.

Established Headquarters of Joint Commission on Accreditation of Hospitals

Announcement from Edwin L. Crosby, M.D., newly appointed Director of the Joint Commission on Accreditation of Hospitals, indicates that the Commission will locate in space which is available through the American College of Surgeons at 660 N. Rush Street, Chicago. It is understood the Commission will be in operation by or before September 1, 1952.

It is announced that the American College of Surgeons will turn over to the Commission all the records which it has accumulated through the years.

New York City Department of Health Tuberculosis Study

A six-man committee of tuberculosis specialists has been recently appointed by Dr. John F. Mahoney, Commissioner of Health for New York City, to determine whether isonicotinic acid hydrazide, one of the new anti-tuberculosis drugs, has a place in public health efforts to control tuberculosis. Among the members of the committee are: Dr. Walsh McDermott, F.A.C.P., Associate Professor of Medicine at Cornell University Medical College and editor of the *American Review of Tuberculosis;* Dr. Edward H. Robitzek, F.A.C.P., Acting Director of Medicine at Sea View Hospital, Staten Island; Dr. H. McLeod Riggins, F.A.C.P., former president of the American Trudeau Society; and Dr. Herbert Edwards, F.A.C.P., Executive Director of the New York Tuberculosis and Health Association. Other members of the Committee are Dr. John K. Lucey, President of the Richmond County Medical Society, and Dr. George W. Mast, Medical Director of the Nepera Chemical Company, manufacturers of the isonicotinic acid hydrazide preparation being used in the study.

Armed Forces Medical Library

The Army Medical Library has recently been redesignated the Armed Forces Medical Library. A joint agency of the three military departments, the library is subject to the authority, direction and control of the Secretary of Defense and is under the management control of the Secretary of the Army. The management authority vested in the Secretary of the Army has been delegated to the Surgeon General, Department of the Army.

Symposium on Military Medicine Held in Waltham, Mass.

A Symposium on Military Medicine was held at the Murphy Army Hospital, Waltham, Mass., June 23, 24 and 25, 1952. Major General George E. Armstrong, F.A.C.P., the Surgeon General, Department of the Army, presented greetings, and many distinguished medical officers of the Army presented papers, among whom were Col. James H. Forsee, F.A.C.P., Fitzsimons Army Hospital, Denver, Colo., "Chest Surgery"; Col. John G. Knauer, F.A.C.P., Valley Forge Army Hospital, Phoenixville, Pa., "Obscure Prolonged Fever of Undetermined Origin"; Col. Robert E. Blount, F.A.C.P., Brooke Army Hospital, San Antonio, Tex., "Malaria"; Col. Fred H. Mowrey, F.A.C.P., Percy Jones Army Hospital, Battle Creek, Mich., "Clinical Aspects of Cold Injury"; Col. Carl W. Tempel, F.A.C.P., Fitzsimons Army Hospital, Denver, Colo., "Treatment of Tuberculosis"; Brig. Gen. Elbert DeCoursey, F.A.C.P., Armed Forces Institute of Pathology, Washington, D. C., "Pathology of Radiation Injuries." Dr. Walter Bauer, F.A.C.P., Harvard Medical School and the Massachusetts General Hospital, Brig. Gen. James S. Simmons, F.A.C.P., Dean of the Harvard School of Public Health, and Dr. Lewis M. Hurxthal, F.A.C.P., Chief of Medicine at the Lahey Clinic, Boston, were guest discussants.

In addition to the regular program, there were a number of scientific exhibits, one on "Total Body Ionizing Radiation," by Brig. Gen. Elbert DeCoursey, F.A.C.P., and another on "Changing Patterns in the Susceptibility of Microörganisms to Various Antibiotics," by Dr. Monroe J. Romansky, F.A.C.P., and others.

Dr. F. M. Pottenger Honored for Tuberculosis Work

Dr. Francis M. Pottenger, a Fellow and co-founder in large measure of the American College of Physicians, was honored by a testimonial dinner given by approximately fifty distinguished medical men at the California Club, Los Angeles, the event marking the Fiftieth Anniversary of Dr. Pottenger's service to the Southern California Anti-Tuberculosis League, which he founded in 1902. Dr. Pottenger is a world figure in the conquest of tuberculosis, and many years ago founded the Pottenger Sanitarium at Pasadena. At this testimonial dinner a series of brief talks by prominent members of the profession was given concerning his past work. Among these speakers were Dr. Egerton Crispin, F.A.C.P., Dr. Carl R. Howson, F.A.C.P., Dr. George Kress, Dr. Francis Pottenger, Jr., F.A.C.P., Dr. B. O. Raulston, F.A.C.P., Dr. E. Kost Shelton, F.A.C.P., Dr. A. H. Weitkamp and the Rev. John Carruthers.

Dr. Pottenger was presented with the first copy of his autobiography, "The Fight Against Tuberculosis," just published by Henry Schuman of New York.

Dr. Pottenger began his medical practice in 1894, after graduating from Otterbein College in Ohio. While establishing his early practice near Cincinnati, Ohio, his wife contracted tuberculosis and this personal tragedy caused him to devote his life to the study of tuberculosis. His relentless attack on this dread disease over more than 50 years constitutes an heroic chapter in the story of modern medicine.

He was for many years a Councillor and Regent of the American College of Physicians, served on numerous committees, and became its President, 1932–33. He was the first physician on the West Coast to devote his whole time to tuberculosis. He was the second man in the United States to occupy a chair for teaching tuberculosis, established in 1902 at the University of Southern California. He became Professor Emeritus of Medicine in 1942.

Dr. Howard T. Karsner Awarded Gold-Headed Cane

The American Association of Pathologists and Bacteriologists recently awarded their Gold-Headed Cane to Dr. Howard T. Karsner, F.A.C.P., of Washington, D. C., for services to humanity. Medical Research Adviser to the Surgeon General of the U. S. Navy, Dr. Karsner was for 35 years Professor of Pathology and Director of the Institute of Pathology of Western Reserve University School of Medicine, Cleveland. He was selected for custodianship of the Cane, which lasts throughout his lifetime, for his early work, which included studies of Hodgkin's disease, cancer of the liver, infarction, diseases of the kidney, and studies of anaphylaxis and anaphylactoid phenomena. Included among his more than 250 publications are textbooks, lectures and monographs.

Georgetown University Alumni Honor Dr. T. F. Keliher

Thomas F. Keliher, B.S., M.D., F.A.C.P., was the recipient of a certificate from the Georgetown University Alumni Club of Washington at its second annual Awards Luncheon held on St. Patrick's Day. One of six alumni to be so honored, Dr. Keliher's certificate read: "The Georgetown University Club of Washington, proudly conscious of the distinguished services rendered by the sons of Georgetown to our country, our city, and our Alma Mater, bestows its Annual Alumni Achievement Award on. . . ." Dr. Keliher is Professor of Internal Medicine at Georgetown University School of Medicine.

Alabama Academy of General Practice Elects Dr. James S. McLester

Dr. James S. McLester, F.A.C.P., Birmingham, Ala., recently became the second physician to be elected to honorary membership in the Alabama Academy of General Practice. The certificate awarded him states that he was elected "an Honorary Member in recognition of his outstanding achievements and contributions to the general practice of medicine."

Citation of Merit to Dr. Charles L. Steinberg

Dr. Charles L. Steinberg, F.A.C.P., Rochester, N. Y., was awarded a Citation of Merit at the annual meeting of the Rochester Academy of Medicine on May 6. The Citation read: "For outstanding contribution to medical science by publications and scientific exhibits and for sharing of his knowledge with his fellow practitioners by his unselfish teachings."

Life Insurance Medical Research Fund Grants

Washington University School of Medicine, St. Louis, Mo., has been awarded a grant of $30,240 by the Life Insurance Medical Research Fund for research on the cellular physiology of acute inflammation by Dr. W. Barry Wood, Jr., F.A.C.P. In addition, $12,530 was granted for research by Dr. Henry A. Schroeder, F.A.C.P., on the influence of the normal and ischemic kidney on the metabolism of amino acids.

Duke University School of Medicine, Durham, N. C., has also received a grant of $22,140 from the Fund for research by Dr. E. A. Stead, Jr., F.A.C.P., on cardiovascular and respiratory physiology, and organ metabolism.

Dr. Orrin Sage Wightman, F.A.C.P., New York City, has become the recipient of the first award of the New York Academy of Medicine Plaque, made in recognition of his extraordinary service to the Academy for a number of years.

Dr. William A. Thornhill, F.A.C.P., Charleston, W. Va., was elected Second Vice-President of the Southeastern Allergy Association at the seventh annual meeting held recently in Augusta, Ga.

At the recent meeting of the California Society of Allergy, held in conjunction with the 81st Annual Session of the California Medical Association, Dr. Norman Shure (Associate), Los Angeles, was elected Secretary-Treasurer.

Dr. Maxwell M. Wintrobe, F.A.C.P., Head of the Department of Medicine, University of Utah College of Medicine, has recently been appointed Chairman of the Advisory Council of the Life Insurance Medical Research Fund for 1952–53.

The Virginia Neuropsychiatric Society, at its annual meeting April 11 in Charlottesville, elected Dr. Granville Jones, F.A.C.P., Superintendent of the Eastern State Hospital, Williamsburg, as Secretary.

Dr. Chester North Frazier, F.A.C.P., Professor of Dermatology, Harvard Medical School, has recently succeeded Dr. William LeRoy Fleming as President of the Massachusetts Society for Social Hygiene.

At the annual Congress of the American College of Allergists, held in Pittsburgh, Pa., April 7–9, Dr. J. Warwick Thomas, F.A.C.P., Richmond, Va., was elected President and Dr. M. Murray Peshkin, F.A.C.P., New York City, was named President-Elect.

Dr. Walter M. Solomon, F.A.C.P., Cleveland, Ohio, was recently named President-Elect of the American Congress of Physical Medicine.

Governor Earl Warren has recently appointed Dr. Norman Reider, F.A.C.P., San Francisco, Calif., to the Advisory Board of the California Advisory Committee on Mental Health.

Dr. Robert F. Loeb, F.A.C.P., Professor of Medicine, Columbia University College of Physicians and Surgeons, has recently been elected to membership on the Council of the National Academy of Sciences, his term expiring June 30, 1955.

Dr. Joseph S. Hiatt, F.A.C.P., McCain, was elected District Councilor for the Fifth District and Chairman of the Section of Medicine at the meeting of the North Carolina State Medical Society, which was held in Pinehurst, May 5–6.

Dr. Lowell T. Coggeshall, F.A.C.P., Dean of the University of Chicago Division of Biological Sciences and Frederick H. Rawson Professor of Medicine, was elected President of the Chicago Society of Internal Medicine at its meeting May 31.

Dr. Mildred C. J. Pfeiffer, F.A.C.P., Philadelphia, has recently been appointed Director of Division of Cardiovascular Diseases of the Health Department of the Commonwealth of Pennsylvania.

Dr. Truman C. Terrell, F.A.C.P., of Fort Worth, was elected President of the Texas Medical Association at its annual meeting in Dallas, May 4–7.

Dr. Henry T. Smith, F.A.C.P., Associate Professor of Medicine, University of Arkansas School of Medicine, was installed as President of the Mid-South Postgraduate Medical Assembly at its recent meeting in Memphis, Tenn.

Dr. Harold J. Jeghers, F.A.C.P., Professor of Medicine at Georgetown University School of Medicine, has been appointed director of a new venture in postgraduate medicine. St. Mary's Hospital, Rochester, Minn., has become affiliated with Georgetown University School of Medicine in order to augment teaching facilities. Under the program, full-time staff members of the School of Medicine will visit St. Mary's monthly for periods of four or five days; residents and interns will be rotated for brief periods through the Georgetown center, and St. Mary's attending staff members will also visit for special instruction and observation.

Dr. Frank B. Queen, F.A.C.P., Professor of Pathology, University of Oregon Medical School, was the guest speaker at a series of cancer lectures held in the eastern part of Montana last month. The series was sponsored by the Montana Medical Association in coöperation with the state board of health.

Under the presidency of Dr. Willard O. Thompson, F.A.C.P., Chicago, the American Geriatrics Society held its annual meeting in Chicago, June 5–7. Among the invited speakers were Dr. Max M. Montgomery, F.A.C.P., Chicago, who presented a paper on "Certain Aspects of ACTH and Cortisone Therapy in Older Patients with Rheumatoid Arthritis"; and Dr. Wright R. Adams, F.A.C.P., Chicago, who discussed "Coronary Artery Disease in the Aged." Dr. LeRoy H. Sloan, Chicago, A.C.P. President-Elect, was the guest speaker at the annual dinner.

At the annual convention of the Catholic Hospital Association of the United States and Canada, which was held in Cleveland, May 26–29, Dr. Thomas P. Murdock, former A.C.P. Governor for Connecticut, and Dr. John J. Grady (Associate), Cleveland, were among the speakers. Their respective topics were "Mutual Understanding Between Administration, Medical, and Nursing Staffs," and "What Is the Responsibility of the Medical Staff for the Educational Program?"

Dr. Charles A. Jones, F.A.C.P., New Orleans, was one of the guest speakers at the annual meeting of the Mississippi State Medical Association, held in Jackson, May 13–15. He spoke on "The Use of ACTH and Cortisone."

Dr. Roland P. Mackay, F.A.C.P., Chicago, presented a paper entitled "Reflections on Memory" at the annual meeting of the Society of Biological Psychiatry, held in Atlantic City, N. J., May 11.

Dr. Arthur L. Bloomfield, F.A.C.P., Professor of Medicine at Stanford University School of Medicine, used "The Principle of Bacterial Infection in the Upper Air Passage" as his topic when he delivered the George M. Kober Lecture in Washington, D. C., May 1.

The annual Colorado Intern-Resident Clinics were held June 4–5 at the University of Colorado Medical Center, Denver. Dr. Tinsley R. Harrison, F.A.C.P., Professor of Medicine at the Medical College of Alabama, was the guest clinician and presented "Some Theoretical and Practical Applications of the Electrokymogram and the Ballistocardiogram."

Dr. Lewis M. Hurxthal, F.A.C.P., Boston, was one of the participants in a seminar on diagnosis, which was held in Jacksonville, Fla., June 19–21.

The New York Society for Circulatory Diseases, meeting June 5 in New York City, heard, among others, Dr. William Hitzig, F.A.C.P., New York, present a paper on "Etiology and the Treatment of Pericarditis."

Dr. Chester M. Kurtz, F.A.C.P., Madison, Wis., was one of the guest speakers at the annual meeting of the Minnesota State Medical Association when it convened in Minneapolis May 26–28. "The Treatment of Convalescent Cardiac Cases" was the subject he discussed.

Dr. Edward Weiss, F.A.C.P., Professor of Clinical Medicine, Temple University School of Medicine, Philadelphia, Pa., was one of eleven out-of-state speakers at the 102nd Annual Session of the Medical Association of Georgia, held in Atlanta, May 11–14. Other members of the College who also participated included Dr. Max Mass, F.A.C.P., Macon; Dr. Ernest F. Wahl, F.A.C.P., Thomasville; Dr. L. Minor Blackford, F.A.C.P., Atlanta; Dr. Harry T. Harper, Jr., F.A.C.P., Augusta; and Dr. Ellison R. Cook, III (Associate), Savannah.

At the Alumni Day Symposium of the Harvard Medical School, which took place at the School on May 28, Dr. Walter Bauer, F.A.C.P., spoke on "Modern Medical Triology"; Dr. Reginald Fitz, F.A.C.P., on "How to Get Your Son into Harvard Medical School"; and Dr. Eugene M. Landis, F.A.C.P., on the "Human Element in First Year Physiology."

Dr. Chester S. Keefer, A.C.P. Governor for Massachusetts, Dr. William B. Castle, F.A.C.P., and Dr. George W. Thorn, F.A.C.P., all of Boston, were among those who collaborated on a symposium on "Present Status of Recent Therapeutic Advances" at the annual meeting of the Massachusetts Medical Society, which was held in Boston, May 20–22. Taking part in a cardiac symposium at the same meeting were Dr. Herrman L. Blumgart, F.A.C.P., Dr. Lewis Dexter, F.A.C.P., and Dr. Laurence B. Ellis, F.AC.P., also of Boston.

"Advances in the Treatment of Tuberculosis" was the topic of Dr. John W. Towey, F.A.C.P., Powers, Mich., when he spoke at clinics held in Janesville, Stevens Point, and Appleton, Wis., in May. The clinics were sponsored by the Council on

Scientific Work of the State Medical Society of Wisconsin in cooperation with the State Board of Health, the Wisconsin Division of the American Cancer Society, Wisconsin Anti-Tuberculosis Association, the Wisconsin Heart Association, the Wisconsin chapters of the National Foundation for Infantile Paralysis, the Wisconsin Academy of General Practice, and the Wisconsin Medical School and Marquette University School of Medicine. Dr. Ovid O. Meyer, F.A.C.P., Madison, addressed similar clinics in Racine, Sheboygan, and Menominee, Mich. His topic was "Therapeutic Use of Cardiac Drugs."

Dr. Edgar R. Pund, F.A.C.P., Professor of Pathology, Medical College of Georgia at Augusta, was one of the guest speakers at the five-day seminar on cancer cytology at the Dade County Cancer Institute Cytology Center, Miami, Fla., April 21–25. The seminar was conducted as part of the one-year anniversary program of the first cytology test made at the Center.

Dr. Samuel G. Feuer (Associate), Brooklyn, N. Y., presented two scientific exhibits at the annual meeting of the Medical Society of the State of New York, held in New York City, May 12–16. One was "Rehabilitation of Hemiplegia" and the other was "Rehabilitation of Amputee." At the meeting of the American Congress of Physical Medicine, to be held in New York City next month, he will present an exhibit on "Rehabilitation of Paraplegia" and will also read a paper entitled "Organization of Rehabilitation Department in a Chronic Disease Hospital."

Dr. Howard F. Rusk, F.A.C.P., Chairman, Department of Physical Medicine and Rehabilitation, New York Hospital-Bellevue Medical Center, addressed the annual meeting of the Health Division of the Welfare Council of Metropolitan Chicago at its meeting, June 9.

Dr. Philip Work, F.A.C.P., has retired from the Veterans Administration and is now engaged in private practice (neuropsychiatry and forensic medicine) at Las Cruces, N. M.

Dr. Charles F. McKhann, F.A.C.P., of Cleveland, has recently been appointed Professor and Head of the Department of Pediatrics at Jefferson Medical College of Philadelphia.

Col. James S. Taylor (retired) (MC), USA, F.A.C.P., has become Chief of the Medical Staff of the Arkansas State Hospital for Nervous Diseases at Little Rock. He had formerly been Chief Cardiologist at Walter Reed Army Hospital, Washington, D. C.

Dr. Wilburt C. Davison, F.A.C.P., Dean, and Dr. Julian M. Ruffin, F.A.C.P., Professor of Medicine, Duke University School of Medicine, together with Dr. Wingate M. Johnson, F.A.C.P., Professor of Clinical Medicine, Bowman Gray School of Medicine of Wake Forest College, were among the group of outstanding medical figures who participated in all-day panel discussions of the President's Commission on the Health Needs of the Nation in Washington, D. C., April 8–10.

Dr. Kenneth Chapman, F.A.C.P., has succeeded Dr. Victor Vogel as medical officer in charge of the U. S. Public Health Hospital, Lexington, Ky. Dr. Chapman was formerly Assistant Chief of the Division of Hospitals of the U. S. P. H. S. in Washington, D. C.

Dr. Hobart A. Reimann, F.A.C.P., Philadelphia, Pa., was a guest of the Pila Clinic, Ponce, Puerto Rico, and delivered lectures in Ponce and San Juan during the week of May 11.

At the Annual Meeting of the American Heart Association at Cleveland during April, following Fellows of the American College of Physicians were elected to office in that Association: Irving S. Wright, M.D., F.A.C.P., New York, N. Y., President; Robert L. King, M.D., F.A.C.P., Seattle, Wash., President-elect; Edgar V. Allen, M.D., F.A.C.P., Rochester, Minn., E. Cowles Andrus, M.D., F.A.C.P., Baltimore, Md., Irvine H. Page, M.D., F.A.C.P., Cleveland, Ohio, and John J. Sampson, M.D., F.A.C.P., San Francisco, Calif., Vice Presidents; William H. Bunn, M.D., F.A.C.P., Youngstown, Ohio, Secretary; Harry E. Ungerleider, M.D., F.A.C.P., New York, N. Y., Assistant Secretary.

OBITUARIES

DR. SAMUEL ALBURTUS BROWN

Dr. Samuel Alburtus Brown died Sunday, March 16, at the Hillsboro Club at Pompano, Florida, at the age of 78. His distinguished career as a physician and medical educator spanned more than half a century. At the time of his death he was Vice Chairman of the Board of Trustees of the New York University-Bellevue Medical Center, a member of the Council of New York University and Dean Emeritus of New York University College of Medicine.

A native of Plainfield, New Jersey, he received his preparatory education in Newark, New Jersey. Dr. Brown entered the University College of Medicine in 1891 and had been continuously associated with the College since that date. He was graduated with the degree of Doctor of Medicine in 1894, served a two-year internship in Bellevue Hospital, and was appointed to the College faculty in 1897 as an instructor in physical diagnosis. In 1926 he was awarded the honorary degree of Doctor of Public Health by New York University.

Dr. Brown served as Dean of the College of Medicine during the years 1916 to 1932, a period of great progress in the medical and basic sciences, which paved the way for the greater strides of modern medicine in more recent years. On relinquishing the deanship of the College of Medicine in 1932, he was appointed to membership in the University Council on April 25, 1932. He was President of the New York Academy of Medicine for the two-year term, 1925–1927, and President of the College of Medicine Alumni Association for the academic year 1923–1924. In 1932, he received the University's Alumni Meritorious Service Award. In addition, his services to the college were commemorated by establishment of the Samuel A. Brown chair of therapeutics, thereby advancing the field of medicine which was his special province.

As a medical educator, he found consummate satisfaction in his advisory rôle in the development and realization of the New York University-Bellevue Medical Center. As Chairman of the Council Committee on Medicine and Dentistry, he was instrumental in convincing the governing Council of the University of the feasibility of that ambitious undertaking and of guiding it into reality. When the Board of Trustees of the Medical Center was established in 1948, he became its Acting Chairman, later assuming the permanent position of Vice Chairman of this Board. In these positions, Dr. Brown played an influential part in the intricate planning of the organizational structure and building program.

For a ten-year period beginning in 1900, Dr. Brown served as assistant surgeon and later surgeon with the 12th Regiment of the National Guard of New York. During the First World War he served in the Army in Washington. He held the rank of Lieutenant Colonel, United States Army Reserve Corps.

As a private practitioner he served over the years a distinguished company of patients, while among the collateral activities he served as consulting physician at Bellevue, New Rochelle, Monmouth Memorial, Long Branch, French, North Hudson, Rockaway, Fitkin Memorial, Harlem, Willard Parker, Nyack, St. Luke's (Newburgh, N. Y.), Polyclinic, and Hackensack hospitals, and was on the board of directors at Doctors Hospital. He was also a consultant for the New York Society for the Relief of Ruptured and Crippled. He was President and a director of Wilbert Realty Corporation, as well as a director of Magnesium Products, Inc., and the Ramsey Corporation.

Organizations in which Dr. Brown held membership include Phi Gamma Delta fraternity, Nu Sigma Nu fraternity, Alpha Omega Alpha, the American College of Physicians, the American Medical Association, the Medical Society of New York, the New York County Medical Society, the New York Academy of Medicine, the

New York Academy of Sciences, Sons of the American Revolution, Museum of Natural History, Harvey Society, New York Society of Military and Naval Officers, American Legion, Reserve Officers Association, Links and Century Clubs.

Dr. Brown resided at Port Washington, N. Y., and is survived by a brother, William P. Brown of Long Island, and two daughters: Mrs. D. Kenneth Rose of Toronto and New York, and Mrs. Frederick T. Pierson, Jr. of Pittsford, N. Y.

CURRIER MCEWEN, M.D.

DR. GEORGE COURTNEY STUCKY, SR.

George Courtney Stucky, Sr., M.D., F.A.C.P., died at Charlotte, Mich., November 26, 1951.

He was born in Louisville, Ky., May 10, 1888. Following graduation from the University of Michigan Medical School in 1923, he was associated with the Henry Ford Hospital in Detroit until 1925. He then became Director and Superintendent of the Ingham Sanatorium, Lansing, Mich., which position he held until 1938 when he became Director of the Eaton County Health Department and held this position until 1948. In 1943 he became Lecturer in Public Health Practices at the University of Michigan School of Public Health and continued in this capacity until his death. In 1947 and 1948 he was President of the Michigan Health Officers Association.

He was a Diplomate of the American Board of Preventive Medicine and Public Health and became a Fellow of the American College of Physicians in 1936.

DOUGLAS DONALD, M.D., F.A.C.P.,
Governor for Michigan

DR. JOSEPH J. ZIMMERMAN

Dr. Joseph J. Zimmerman, an Associate of the College since 1949, died on October 11, 1951, of a heart attack at his home in Philadelphia. He was born December 29, 1914, received his A.B. degree in 1935 and his M.D. degree in 1940 at the University of Pennsylvania. He interned at the Philadelphia General Hospital, 1940–42, and served at the same institution as a Resident, 1942–44. Since 1946, he was a Clinical Assistant at the Philadelphia General Hospital and, since 1948, Ward Assistant at the Graduate Hospital of the University of Pennsylvania. He had also been an Instructor in Medicine at the University of Pennsylvania School of Medicine, and an Assistant Instructor in Medicine at the University of Pennsylvania Graduate School of Medicine.

Dr. Zimmerman was a member of the Philadelphia County Medical Society, Blockley Medical Society, Medical Society of the State of Pennsylvania, and American Medical Association.

MINUTES OF THE JOINT EXECUTIVE SESSION OF THE BOARD OF REGENTS AND BOARD OF GOVERNORS

CLEVELAND, OHIO

APRIL 20, 1952

A combined Executive Session of the Board of Regents and Board of Governors of the American College of Physicians convened at two o'clock at the Public Auditorium, Cleveland, Ohio, April 20, 1952, preceding the opening of the Thirty-third Annual Session. President Maurice C. Pincoffs presided, Mr. E. R. Loveland was Secretary, and the following were in attendance:

Officers and Regents:

Maurice C. Pincoffs	President
T. Grier Miller	President-Elect
LeRoy H. Sloan	First Vice President
Walter B. Martin	Second Vice President
Howard P. Lewis	Third Vice President
William D. Stroud	Treasurer
Richard A. Kern	Secretary-General
Edward L. Bortz	
Harold H. Jones	
Charles F. Moffatt	
A. B. Brower	
Alex. M. Burgess	
George H. Lathrope	
Cyrus C. Sturgis	
Marion A. Blankenhorn	
Asa L. Lincoln	
J. Owsley Manier	
Walter L. Palmer	
Wallace M. Yater	
Charles A. Doan	Chairman, Board of Governors
George Morris Piersol	Chairman, Committee on Credentials

Governors:

Leland Hawkins, Los Angeles	CALIFORNIA (Southern)
Ward Darley, Denver	COLORADO
*John C. Leonard, Hartford	CONNECTICUT
John Minor, Washington	DISTRICT OF COLUMBIA
Charles H. Drenckhahn, Urbana	ILLINOIS (Southern)
James O. Ritchey, Indianapolis	INDIANA
William C. Menninger, Topeka	KANSAS
Chester S. Keefer, Boston	MASSACHUSETTS
Joseph D. McCarthy, Omaha	NEBRASKA
Edward C. Reifenstein, Sr., Syracuse	NEW YORK (Western)
Wann Langston, Oklahoma City	OKLAHOMA
*Edward L. Bortz, Philadelphia	PENNSYLVANIA (Eastern)

* Alternate.

Charles W. Morton, Pittsburgh .....PENNSYLVANIA (Western)
William C. Chaney, Memphis .....TENNESSEE
Fuller B. Bailey, Salt Lake City .....UTAH
Nils P. Larsen, Honolulu .....HAWAII
Herbert K. Detweiler, Toronto .....ONTARIO
*Cornelius DeW. Briscoe, Panama .....REPUBLIC OF PANAMA and the CANAL ZONE
Stacy R. Mettier, San Francisco .....CALIFORNIA (Northern)
Benjamin F. Wolverton, Cedar Rapids ....IOWA
Thomas Findley, New Orleans .....LOUISIANA
Douglas Donald, Detroit .....MICHIGAN
Wesley W. Spink, Minneapolis .....MINNESOTA
Ralph A. Kinsella, St. Louis .....MISSOURI
Harry T. French, Hanover .....NEW HAMPSHIRE
Edward C. Klein, Jr., South Orange .....NEW JERSEY
Elbert L. Persons, Durham .....NORTH CAROLINA
Robert B. Radl, Bismarck .....NORTH DAKOTA
Robert Wilson, Jr., Charleston .....SOUTH CAROLINA
Ellsworth L. Amidon, Burlington .....VERMONT
Charles M. Caravati, Richmond .....VIRGINIA
George H. Anderson, Spokane .....WASHINGTON
Paul H. Revercomb, Charleston .....WEST VIRGINIA
*E. H. Mason, Montreal .....QUEBEC
Jose J. Centurion, Havana .....CUBA

*D. O. Wright, Birmingham .....ALABAMA
Leslie R. Kober, Phoenix .....ARIZONA
Lemuel C. McGee, Wilmington .....DELAWARE
William C. Blake, Tampa .....FLORIDA
Carter Smith, Atlanta .....GEORGIA
Howard Wakefield, Chicago .....ILLINOIS (Northern)
J. Murray Kinsman, Louisville .....KENTUCKY
Richard S. Hawkes, Portland .....MAINE
R. Carmichael Tilghman, Baltimore .....MARYLAND
Laurance J. Clark, Sr., Vicksburg .....MISSISSIPPI
Harold W. Gregg, Butte .....MONTANA and WYOMING
Walter I. Werner, Albuquerque .....NEW MEXICO
Irving S. Wright, New York .....NEW YORK (Eastern)
Karver L. Puestow, Madison .....WISCONSIN
*J. F. Elliott, Edmonton .....ALBERTA and BRITISH COLUMBIA
Charles H. A. Walton, Winnipeg .....MANITOBA and SASKATCHEWAN

*Dan C. Ogle .....UNITED STATES AIR FORCE
George E. Armstrong .....UNITED STATES ARMY
H. Lamont Pugh .....UNITED STATES NAVY
*Myron D. Miller .....UNITED STATES PUBLIC HEALTH SERVICE
*Arden Freer .....UNITED STATES VETERANS ADMINISTRATION

PRESIDENT MAURICE C. PINCOFFS: "We have a matter of very important policy for the College to discuss, and I propose that we make it the main order of business.

*Alternate.

First on our Agenda is the reading of the abstracted Minutes of the last meeting of the Board of Regents and the last meeting of the Board of Governors."

. . . It was moved, seconded and carried that the reading of the Minutes be dispensed with, inasmuch as they had been published in the Annals of Internal Medicine . . . .

PRESIDENT PINCOFFS: "The important matter to determine concerning policy relates to the Doan Committee report and to the deliberations of the Regents' Committee concerning the report. There is in that report a matter which, if both the Governors and Regents act this afternoon, can legally be presented as an amendment to the By-Laws of the College at the Annual Business Meeting on April 24; but if we should be unable to reach a decision this afternoon, it would, perforce, have to wait over for another year. I have become aware, and I think most of you have too, in traveling about the country at various Regional Meetings, the College membership is a little unrestful over the indecision in regard to this matter. I propose, therefore, to review the status of this matter briefly and then to ask the Chairman of the Board of Governors to convene the Governors for their action and recommendations. Following this, I shall convene the Regents present to see how they may wish to act upon what comes to them from the Governors.

"Briefly, you will remember that the Board of Governors appointed a Committee under Dr. Charles A. Doan which, after study and a really very able report, concluded by recommending:

'(1) Certification by the American Board of Internal Medicine, or an allied board, shall be a prerequisite for election to Associateship;
'(2) There shall be no limit to the term of Associateship;
'(3) Associates shall (a) have been Associates at least three years and (b) shall show evidence of progressive professional attainment and advancement before consideration for election to Fellowship.'

"That report passed the Board of Governors with only one dissenting vote and was referred to the Regents. At the first meeting of the Regents after that—on Friday at the St. Louis Session, 1951—the President, with the assent of the Board of Regents, appointed a Committee to consider this report from the Governors and to recommend action to the Board of Regents. That Committee consisted of Dr. LeRoy H. Sloan, Chairman, Dr. T. Grier Miller, our President-Elect, Doctors J. Owsley Manier, Roy R. Snowden, Charles A. Doan and your President, ex officio. The Committee met on two occasions and discussed at great length the pros and cons of this rather complex situation. At its meeting last November, it made these recommendations to the Regents:

'(1) Certification shall not be a prerequisite for Associateship.'

"In other words, that matter shall remain status quo—where it is a prerequisite to Fellowship, but not to Associateship.

'(2) Term of Associateship shall be from three years to a maximum of ten years;
'(3) The Governor shall have certain directives, including the appointment of a committee of three to five members with staggered terms, each member to serve not more than five consecutive years; said committee to work with the Governor in assessing the progress and qualification of Associates, to be obtained from a form devised for an annual report from each Associate.'

"This was moved and received by the Board of Regents and returned again to the Board of Governors for their further consideration and recommendation. In essence it is a counterproposal from the Regents back to the Governors. Now, that part of

it which could be made effective at your pleasures, Governors and Regents, is that which relates to the term of Associateship. Before asking the Chairman of the Board of Governors to convene that body to consider these matters, I would like to say a word, as President, as to my own reactions and opinions concerning these three items, particularly that which should be, I think, the center of this afternoon's discussion, namely, the lengthening of the term of Associateship.

"I believe strongly in the lengthening of the term of Associateship. I do not feel that five years gives a man sufficient time, in many instances, to demonstrate the higher qualifications requisite for proper election to Fellowship. I believe that to retain the term at five years is something of an impediment to raising the qualifications for Fellowship. I believe as the number of men practicing Internal Medicine becomes several times as large as it is now, within the next ten to fifteen years, if the College is to maintain prestige, it must progressively become more selective. If it is to have higher qualifications, a gradual increase in qualifications, a closer scanning of its Associate membership, then I believe it must give to the Associate more time to demonstrate his ability to progress medically and in status in his community, before we say that he has failed to meet the requirements.

"I believe that this third recommendation of the Regents' Committee, which in essence means that we amplify our mechanism for the study of men prior to election to Associateship and particularly later, prior to their advancement to Fellowship, should be very much in favor. We amplify it here by placing more responsibility first on the Associate himself, in that he will be required to furnish annually a report of progress. Naturally, this is not the time to specify what items should be reported on, but I think it is obvious to us all that there are a great many items to report on beyond his publications and beyond the matter of his teaching or research. It amplifies it also by giving to the Governor an advisory group with whom to confer on these records. Perhaps the Governor's advisory group will interview the candidates who are coming up for Fellowship.

"As far as the business of the afternoon, however, it is my opinion that there are many questions here that are unsettled. 'The Governor shall have certain directives,' but I confess that after studying the Constitution, I am not too certain at the moment just what these directives could constitutionally come from. In other words, while I approve of this entirely in principle, I would hope that nothing more than its approval in principle and the delegation to put it into form should be as far as this meeting this afternoon should go.

"Now, going back to the first recommendation—'Certification shall not be a prerequisite for Associateship,' as opposed to the Governors' recommendation that it shall be. There is so rapid an increase in the number of candidates for Associateship who have already obtained certification that I think the matter is in process of solving itself. There is required no change in the By-Laws for that, so I do not feel it is crucial that any decision on that matter be made this afternoon. I think that could well be considered at greater length in the next Governors' meeting and come up in due course of channels.

"So, in brief, my hope is that because of the value of some action at this Annual Session that we shall be able to come to a decision on this increase of the Associate term from a maximum of five years to a maximum of ten years, that we may get some guiding movement, after approval in principle, on the new addition to the Governors' duties in relation to proposal for advancement, and I think the other could very well be deferred.

"I am now turning the conduct of the meeting over to Dr. Charles A. Doan, Chairman of the Board of Governors, to convene the Governors in session and to carry on to see what their wishes are."

. . . Doctor Doan took the Chair. . . .

DR. CHARLES A. DOAN: "The Board of Governors, in the presence of the Board of Regents, will convene on this specific agenda and order of business which has been outlined to us by President Pincoffs.

"There was unusual unanimity on the part of the Board of Governors a year ago that certain changes probably would be of advantage to the College in terms of its membership and the composition of its membership. The recommendations which were forwarded by the Governors to the Regents resulted in the appointment of a Committee. Its membership, with Dr. Sloan as Chairman, has been announced. The deliberations of the Board of Governors, in terms of these matters, received consideration at two rather lengthy sessions of the Regents' Committee, and the Minutes, essentially unabridged, of these deliberations were printed in the ANNALS OF INTERNAL MEDICINE in January, 1952. On the date of March 5, 1952, I sent a letter to each Governor, asking that these Minutes of the deliberations of the Regents' Committee be considered by you individually and that insofar as possible there be a discussion with your respective constituencies with reference to these matters, and pointed out there would then be an opportunity for discussion with reference to the counterproposals that are coming back to the Board of Governors from the Board of Regents, in line with the recommendations of the Regents' Committee. Those you are familiar with.

"To promote the discussion and consideration that is desired at this time, reserving certain auxiliary items to our Business Meeting on Thursday, I should like to bring to your attention for consideration, first, the second point that was recommended by the Regents' Committee, namely, that the term of Associateship be maintained at a minimum of three years, but be extended in terms of the maximum period to ten years.

"This general matter has been under discussion repeatedly for a number of years. There was a feeling on the part of the Governors that there had been a good deal of discussion and, admittedly, a good deal of opinion, but perhaps some action should be taken so that we would have this particular change either approved or disapproved by the membership, in the light of the progress of medicine as it is occurring in this country at the present time.

"Consequently, rather than read excerpts from the letters I have received from many of you, which I have appreciated and which can be a background for our meeting on Wednesday, I shall present to you for discussion this one particular recommendation from the Regents' Committee that has to do with the extension of the period of Associateship from the present five-year limit to ten years.

"I will simply say that in the discussions we had in the Regents' Committee that we finally arrived at this compromise. It represents as nearly as possible a unanimous recommendation from that Committee. It seemed to us that it would meet as nearly as possible the two extreme points of view; first, that there should be a definite limitation to Associateship, rather than considering membership permanent—so that it was desired to have the Associateship just one hurdle in a two-hurdle race, at least to become a Fellow and thereafter a permanent member of the College.

"On the other extreme was that of an indefinite membership which could be conferred upon Associates, and that once a man was thought to be worthy of Associateship in the College, he could retain it permanently, or he would only have to prove himself in terms of extraordinary accomplishments to be elected to Fellowship and subsequently to Mastership. With there being as many points of view as would be expected among physicians and citizens of this country, this compromise, which partakes of both of the factors, is presented now for your discussion and consideration."

DR. WARD DARLEY: "I move that the recommendation of the Committee on this particular point be accepted by the Board of Governors."

Dr. Howard Wakefield: "I second the motion. My own personal opinion is that there should be this limitation to Associateship; that it certainly should not be an indefinite period. I have sampled a good many opinions in my own area, both among the younger men who are Associates and among those who are Fellows. Many are in leading positions in our schools and hospitals, and I found no one who approved of the indefinite period. In my own mind, I have not reached a conclusion as to how many years should constitute the maximum Associateship—maybe a compromise of seven or eight years might be better. This is a new move, and experience may prove that ten years may not be necessary. We are flexible, our wisdom is wide and we can always change. The other thing I learned, in talking to my younger constituents, is that even though the maximum Associate period may be extended to ten years, many will still qualify for Fellowship in the three-year limit, and plenty of them between four and five years. I know there are many personal justifications for the wisdom and sound philosophy of giving some of these younger men a little longer period in which to grow and to mature."

Dr. Harry T. French: "If a period of five years was found adequate for most of the candidates previous to the war, then the probability would be that as we return to more normal conditions, we would again find that the five-year period provides enough preparation for most of the Associates to qualify for Fellowship."

Dr. Elbert L. Persons: "Mr. Chairman, I feel this is a very radical step for the College to be taking at this time. Doubling the period from five to ten years is going to be very difficult to explain to our membership. I seriously doubt whether it is necessary. The Board of Regents has been extremely generous in allowing men extra time in their five-year periods when specific and adequate reasons came up. I believe it is almost the rule, although not invariable, that any man who is going to be able to qualify for Fellowship will qualify within five years or less. Doubling this period now would be a great mistake and would be very difficult to explain to our membership. At the most, I would favor a seven-year term instead of a five-year term."

Dr. Karver L. Puestow: "Mr. Chairman, this matter has been up for a long time. There have been many conflicting opinions pertaining to ways and means whereby it should be handled. Now we are at the point where we are ready to move, and that move is to extend the period of Associateship for a questionable number of years. It seems to me if we would restrict our considerations now to an expression as to whether or not we want the Associateship period extended, we can in a subsequent motion determine how many years we want to extend it, and then finally determine how it is to apply and be interpreted."

Chairman Doan: "Dr. Puestow, there is a motion before the house which would need to be voted down and a substitute motion made, with reference to modification that you mentioned; at the moment we are discussing a motion which is before the Board of Governors approving in principle and length of time the extension of Associateship."

Dr. Puestow: "I would like to make a motion to amend the present motion, to the effect that we consider first the question as to whether or not Associateship shall be extended at all—leaving out the number of years until after the amendment has been voted upon."

. . . The motion was seconded by Dr. Ellsworth L. Amidon and opened for discussion. . . .

Dr. Richard S. Hawkes: "Before a vote is taken on this matter, I would like to ask if it is not one of the reasons for bringing this whole matter up, to limit to some degree the size of the College? Perhaps any extension of the period of Associateship would have the other effect upon the size of the College—would considerably increase the number of Associates."

CHAIRMAN DOAN: "We haven't any statistics upon the matter, but some do not think it would appreciably affect the size, certainly not permanently. The selection of Associates and Fellows would ultimately be correspondingly adjusted."

DR. LESLIE R. KOBER: "Speaking from a state in which we have no medical school, I would like to recommend the longer term, either eight or ten years, because, we have a number of men who might qualify for Associateship, but in order to progress they will have to travel outside of the state and might readily need a longer period than five years. It is rather difficult for the young man to travel far to get his postgraduate work. If the College Sessions are held in the East, it is a long trip for him to take to attend the meetings. Some of our men would have difficulty in achieving Fellowship in five years. We now insist that they have practically all the qualifications for Fellowship before coming in as Associates."

DR. JOHN MINOR: "I would simply like to say I am in favor of the extension of the Associate term. It does nothing to the men who are able to qualify in three years or five years, but it does give an opportunity to men whom we all see as Governors who for many reasons, and valid ones, cannot meet to our satisfaction the degree of development in growth required for Fellowship in five years."

DR. RALPH A. KINSELLA: "In the years that I have been Governor, and I have been one for a long time, I have never seen an instance in which a man failed to become a Fellow in five years, with all the urging that goes out from the central office, for him to develop the requirements for Fellowship in the required time. It seems to me it is a mechanical arrangement, whether it be five or eight years; the problem is just the same. As far as my constituency is concerned, the ones that failed never would have qualified."

DR. JOSEPH D. MCCARTHY: "Mr. Chairman, it seems to me there is a bit of procrastination in most of us. Perhaps some extension is needed, but I would favor an extension in terms that would be the closest to five years. The longer the term is made the longer some men will procrastinate. I even predict that if the term were extended to fifteen years, we would have just as many failing to qualify, and perhaps more, than we have in five years."

DR. EDWARD C. KLEIN, JR. "Last year we practically unanimously went on record as approving a permanent Associateship. Now, one year later, some of us are objecting even to the addition of a maximum of ten years. In speaking in New Jersey among some of the members, the idea of a permanent membership was heartily opposed, in view of the fact that it would sort of set up a class-type of membership. On the other hand, an extension of the maximum term from five to ten years has been generally acceptable. I would like to go on record as favoring the recommendations of the Regents' Committee, ten years."

DR. AMIDON: "As a compromise, I wonder if it might not be well to consider having this an indefinite period for perhaps a year or two? Many of us cannot be sure just what the effect is going to be. Many here have expressed opinions which we more or less agreed with. If we leave it indefinite at this time, would not a year or two possibly decide what is the proper period?"

CHAIRMAN DOAN: "I interpret this recommendation from the Board of Regents to be just that. It does make it indefinite for the next few years, in the sense of making it ten years. There is the feeling on the part of many Governors who have to face Associates who are dropped at the end of five years, even with what seems to them because of good reasons—it has been embarrassing for the Governors to have some of these very conscientious men dropped. The current recommendation is a step toward accomplishing the universality of our objectives and ideals, to bring postgraduate training continuously to a large number of men."

DR. WALTER B. MARTIN: "As a point of information, the Board of Regents did not recommend ten years. Their Committee recommended to the Board of Regents the ten-year period."

PRESIDENT PINCOFFS: "That was stated, Dr. Martin. In other words, to back up what Dr. Martin said, I think it should be clear that the Board of Regents did not decide affirmatively that this was their program. They considered it at length and then returned the Committee recommendation to the Board of Governors to get its reaction. I would like to repeat, there is no desire, certainly on my part as President, to try to put pressure to rush through anything as important as this. It is simply my hope that out of this session we may take some definite action. Unfortunately, or fortunately, as you may look at it, we have to proceed under the terms of our Constitution and By-Laws. This matter was presented to the Regents in writing, in due form, not thirty days, but six months before, and so it meets the requirements for amendment. If passed in this form by the Governors and subsequently by the Regents, it can be voted upon by the membership as a whole on Thursday. Amendments to it would, of course, mean that we would have to wait another year before any action could be taken."

CHAIRMAN DOAN: "Are you ready for the question? The motion before the Board of Governors is that Associateship be extended from the minimum of three years, which is not a change from the original, to a maximum of ten years. The amendment to the motion is that there be an extension of time without specific number of years, but that the amendment be first voted upon with reference to any extension at all."

. . . The amendment was put to vote and carried almost unanimously. Then the motion to extend the Associate term maximum to ten years was put to vote and carried, 39 to 13. . . .

CHAIRMAN DOAN: "We shall now consider the recommendation from the Regents' Committee that the Board of Governors approve in principle that each Governor shall have an Advisory Committee in his territory, with the specific duty of helping him in the appraisal of candidates for Associateship and of Associates for advancement to Fellowship. This is already being done in some of the larger centers, such as Eastern New York and Northern Illinois. Certainly in Ohio it wouldn't be possible for me, as Governor, to act in the true capacity if I didn't have representatives to furnish me confidential advice on specific candidates. This proposal would be a matter that would become a matter of record, whereas now it is a matter of option. This would be a recommendation to the Board of Regents from the Board of Governors that this principle would be considered a helpful move in the direction of the selection of those who shall first attain Associateship and later achieve Fellowship. That would imply probably the maintenance of a running record of each Associate, so that an annual inventory of his activities for each year would be available to the Committee for appraisal of his progress toward Fellowship."

DR. WAKEFIELD: "Mr. Chairman, the Regents have emphasized the importance of selectivity. We, as Governors at the state level, and all of our colleagues are in the most strategic position to evaluate a man in medicine. We should use all the resources available. I am strongly favorable toward this confidential or anonymous Advisory Committee. My committee are men of vision. They are impartial; I can depend on their opinions one hundred per cent, but I keep the personnel of this committee confidential. This local Advisory Committee, of five or six men, is of tremendous value to the Governor in the evaluation of candidates.

"Now, there is one procedure that I have instituted in the Chicago area about which not only I, but also our Associates are enthusiastic. Both the original and the duplicate copy of proposal forms naturally come to my desk for endorsement. If I don't know the candidate, or if I am not satisfied by the written record, I call the candidate in by personal invitation or telephone for an informal interview, or I may ask him to write a report to me in his own way, outlining how he has grown and how he has fulfilled the requirements. I ask them, 'how do you spend your time?

What is your program? How much time in practice? How much time in hospitals? What is your teaching program? What are your plans in the next three to five years?' I have been quite surprised at some wonderful clinical ideas these men have to pursue and how they are going to do it in their own way. Our conversation also brings out the cultural and spiritual activities they are carrying on. I point out that this matter of growth is not just writing scientific papers. It is serving on committees in the medical society. It is doing some civic job. It reaches out in many directions. That is why I am skeptical at the moment of a standardized form."

CHAIRMAN DOAN: "Dr. Wakefield has emphasized the importance of this Advisory Committee for the big cities. I think it is just as important in the states where communities are smaller. They get the feeling of being individuals, knowing they are being considered by a committee, even though they don't know the personnel."

DR. HAROLD W. GREGG: "Mr. Chairman, I believe this is a very important step forward. Our territory extends about a thousand miles. It is almost impossible for a Governor to keep up with the different candidates for membership. Are they men of integrity in their community? What are they doing? How are they qualifying? I could not tell without an Advisory Committee. We have used it informally, and I think it should be used formally."

DR. EDWARD C. REIFENSTEIN, SR.: "Ever since I have been Governor, I have been putting into practice what is recommended today through an Advisory Committee. We have a rotating committee. Its personnel is secret. Under the present setup it is often impossible to use the committee as you wish to. Proposals may reach me two days before they are due at Philadelphia, in order to meet the time limit for action at the forthcoming meeting of the Committee on Credentials. I don't have time always to consult my committee as I would like to. I feel the Governors should have at least a month after receipt of a proposal before he needs send it in to the Central Office. I would like to make such a motion, slightly changing the motion now before the Board, namely, that the several Governors shall have rotating Advisory Membership Committees in their territories, appointed by the Governor, preferably selected from localities in which members are situated; further, I move that proposals for membership shall be completed and placed in the hands of the respective Governors for at least one month for investigation before they need be forwarded to the Central Office of the College."

DR. WILLIAM C. MENNINGER: "I second the motion."

DR. JAMES O. RITCHEY: "Do you have in mind that the names of this Advisory Committee be officially in the files, or is this rotating committee just your own helpers?"

DR. REIFENSTEIN: "I find that men will tell me things confidentially over the telephone that they will not write about. They don't want to be on record. I get more information over the telephone than I do by correspondence. I have files for all of the Associates. It would be my idea that we continue those files as a permanent record and have reports made once a year to my office concerning the progress of the Associates during that period."

DR. MINOR: "I question the necessity of formulizing the utilization of people in your own community in this way. I am against formulization. I am not at all sure it is necessary. Every Governor who is conscientious, and as far as I know one hundred per cent of ours are, uses these methods all the time. If they don't they are not performing the office of Governors.

"If it is going to be an anonymous committee, you don't need formulizing. It is simply the understanding that we can utilize, as we already do, those people in our community who would know about these particular candidates. It seems to me the more rules we have the more trouble we get into. Simple inquiries, a yearly check-up, organized in some suitable fashion from the Central Office, are all that is necessary. I question the necessity for formulizing that motion."

CHAIRMAN DOAN: "When I first took over the responsibilities as Governor for Ohio there was no direction with reference to how my duties should be done. My predecessor, Dr. A. B. Brower, told me what he had done, which was a tremendous job. I think the thought is to have instructions to new Governors as they come in to positions of responsibilities in their states, familiarizing them with the principles carried out elsewhere and found to have been helpful. I do not think it is the intent of the motion to formulize to the point of making it necessarily a rigid mandatory rule to be carried out exactly the same in every state by every Governor. It would, however, put on record, as the President stated earlier in this meeting, something of the duties and obligations, prerogatives and privileges of the Governors, which the present rules and regulations do not specify in any way.

"We have tried to overcome that in recent years by establishing an orientation meeting for the new Governors immediately after their election, to give them some suggestions from those who have had earlier experience. The present proposal is just to give one more source of advice and of suggestion of how things might best be done in terms of the College."

DR. PALMER: "Is this committee to be appointed by the Governors as they come into office, or is this committee to continue on after a Governor has retired and serve with the incoming Governor? I can visualize how an incoming Governor might find himself saddled with a committee which he didn't like. I think the Governor should have the privilege of choosing his own committee."

CHAIRMAN DOAN: "The committee ought to be his own cabinet. That, however, was not implied in the motion and, therefore, would be left open as far as any directive."

DR. RITCHEY: "This motion means it would be a formulized Advisory Committee."

CHAIRMAN DOAN: "This is a recommendation from the Board of Regents. The Governors' action is directed towards approval in principle of their suggestion. Our action goes back to the Board of Regents for final action and implement."

DR. KLEIN: "I also thought of the possibility of this proposal saddling a Governor with a committee that would not be of his own choosing. As Dr. Minor said, if a Governor isn't doing the job he should do, it is because he was not properly instructed in the first place. When I became a neophyte Governor my predecessor, Dr. George H. Lathrope, indoctrinated me; but, to formulize it and make a mandate that it be in the form of the records to have an Advisory Committee, be it secret or announced, I think is tying the Governors' hands. The principle is different for different localities, different states, different Governors, and each Governor has to use means that are best available for him in his own community. Don't give us a group or committee of Lord Governors. That would be merely instigating the viewpoint that we are not able to do the job ourselves. Informally we are using such methods, but do not make it a legal mandate."

DR. LEROY H. SLOAN: "Mr. Chairman, the Committee worked for many, many hours on this whole proposition. Discussion of the Governors now is carrying on far beyond the ideas of the Committee. There is no mandate. The Governors are asked to approve in principle only in order that the Board of Regents may begin to develop some sort of a plan or system for the better determination of the candidate's fitness to become an Associate or Fellow. The Board of Regents hopes to develop some sort of a plan whereby we can say that the candidate is not only qualified educationally and professionally, but qualified in all other terms to become a member. I assure you there will be no legal mandate to any Governor to do this, that or the other thing. He still will have the right to do it the way he wants. He will only be given suggestions as to how it might possibly be done."

PRESIDENT PINCOFFS: "I would like to back up what Dr. Sloan has said about the tentativeness of this paragraph. The discussion from the Governors has been very

helpful and very stimulating in showing the care many of you take. It is a strange fact that in our Constitution and By-Laws, if you try to determine what the obligations, authority and scope of work of a Governor is, you would find it extremely difficult to do so. Governors have moved by tradition and custom, and there is now this one way of passing it on formally through this very brief single indoctrination meeting. I do not think that is very adequate. Some of these things are solely principles of the responsibility of the Governor, the greater responsibility of the Governor for keeping records on his Associates and for using advisers in determining them, the greater weight given to that recommendation ought, after careful thought to the wording so that it cannot handicap him in any way, to be embodied somewhere in the written laws of the College. It is a real step forward, I think, to get away from the very large responsibility put solely on a central Credentials Committee, and to give it this very important aid from the people who are closest to the candidate. I merely wanted to bring out that there are really two parts to this proposal on which we hope to have approval in principle. One is the general principle of advisers to the Governor, and the other is the principle of the responsibility of the Associate, of furnishing the Governor with some type of progress report, so that he carries a little of the responsibility of thinking yearly of what he has done, and furnishes the Governor something tangible to work on. I believe these should be approved by you in principle. They will certainly receive very careful consideration from the Regents."

CHAIRMAN DOAN: "The question has been called for. The motion is that, in principle we approve the adoption of advisory help to the Governor with reference to the selection of Associates and the endorsement for Fellowship in the College, with the details to be further considered by the Board of Regents in terms of the discussion they have heard today, in terms of discussions they have already had in their own deliberations, in terms of a problem which is increasingly difficult and complex, in terms of the Committee on Credentials.

"It has been suggested also that there be a change in the modification of deadlines for the Governor to forward proposals to the Central Office, in order to give him opportunity to exercise his personal and joint investigation before submission of proposals to the Philadelphia Office. This latter point should be made known to the membership generally, so that we can do a more careful job, both individually and with the candidates we choose for the duration of our terms as Governors."

. . . The motion was put to vote and carried unanimously. At this point Chairman Doan declared the meeting of the Board of Governors adjourned, and President Pincoffs resumed the Chair and then proceeded to reconvene the meeting of the Board of Regents. . . .

PRESIDENT PINCOFFS: As the first item on this Agenda of the Regents, I shall ask consideration of the recommendation we have just received from the Board of Governors, namely, that the maximal term of Associateship be lengthened from five to ten years."

DR. WALLACE M. YATER: "I move that the Board of Regents approve the extension of the maximal term of Associateship from five years to ten years, and that the Committee on Constitution and By-Laws prepare the amendment and present it at the Annual Business Meeting of this College on Thursday, April 24, 1952."

DR. CYRUS C. STURGIS: "I second the motion."

PRESIDENT PINCOFFS: "It is now opened for discussion."

DR. MARTIN: "I am entirely in favor of lengthening the term. It is a rather radical step when we double the time. It has bothered me to the extent that I think it probably would be a more conservative move to extend it only to eight years. If experience taught us that was the desirable time, or that it was not sufficiently long, we could change it again later. Personally, I would be in favor of eight years rather than ten years."

DR. ALEX. M. BURGESS: "I take the opposite point of view. I am strongly in favor of ten years, for all the reasons given. I feel there are excellent people who have found for personal reasons it wasn't possible for them to accomplish everything that would qualify them in five years for Fellowship. I do not think the extra five years does anybody any harm; the more rapid people can still do it in three years."

PRESIDENT PINCOFFS: "The question is called for. If there is no further discussion, we shall call for the vote."

. . . The motion was put and passed. . . .

PRESIDENT PINCOFFS: "Interpretation of the application of this amendment is a matter of next decision by the Board of Regents. It is important that there be an announcement of the full interpretation of this change. Perhaps the Board of Regents will authorize their President, preferably their incoming President, to appoint at once a committee to outline a careful interpretation, the committee to be composed of regional representatives and certainly some Governors, and to publish the interpretation as soon as possible in the ANNALS. This is merely a proposed modus operandi submitted to the Regents for discussion."

DR. HOWARD P. LEWIS: "Mr. President, it seems to me that this resolution has no bad effect on any present incumbent Associate. It will do him no harm in any way. He can still qualify in the minimum of three years. I think this amendment should be implemented immediately."

DR. PALMER: "I want to support the point of view taken by Dr. Lewis. It would seem grossly unfair to drop from the College now anybody who has failed to qualify simply because of the five-year period."

PRESIDENT PINCOFFS: "You mean 'now' in the sense of the action taken by the Committee on Credentials?"

DR. PALMER: "I would think so. If the Committee on Credentials is to report this afternoon to the Board of Regents on individuals who are dropped because of the expiration of their five-year term, I would consider such action to be grossly unfair."

PRESIDENT PINCOFFS: "Of course this matter we have just passed on, both by the Regents and Governors, is not the law of the College until Thursday, April 24, 1952, and then only if the majority of the Fellows support it. We are still working under the old By-Laws. We could, of course, defer action, if it seems to the Regents that action on the dropping of members should be deferred until later."

DR. STURGIS: "I would like to move that no action be taken at this meeting of the Board of Regents on the dropping of those who have failed to meet the requirements in five years."

DR. MCCARTHY: "Some have already resigned, fearing to be dropped. What happens to those?"

PRESIDENT PINCOFFS: "We could refuse to accept their resignations. Some of these, however, have resigned previously, last November. We cannot be unfair to either of these groups. The committee that works out the interpretation of the amendment must take into consideration all of these interested cases. May we have a vote on Dr. Sturgis' motion?"

. . . The motion was put to vote and carried. . . .

PRESIDENT PINCOFFS: "The Committee on Public Relations will report on resignations at the Tuesday meeting of the Regents. I am sure that the action of the Board of Regents will authorize letters to those who have resigned because they could not meet qualifications within the specified time, advising them that their resignations may be withdrawn."

DR. MARTIN: "Mr. President, I foresaw some of the difficulties that would come up when we implement this amendment. A committee for that purpose should be appointed now and should bring back a report by the Tuesday meeting of the Board of Regents."

PRESIDENT PINCOFFS: "A report brought to the Regents on Tuesday would enable us to announce a policy to the College at the Annual Business Meeting when this amendment is presented. I will assume the responsibility of appointing such a committee to prepare recommendations to the Regents, and I name Dr. Walter L. Palmer, Dr. Charles A. Doan and Dr. Walter B. Martin.

"Let us proceed to some discussion of what we should do in view of the Governors' recommendations, in principle, as to establishing a method by which the incoming Governor will have an adequate outline of his duties and procedures—not rigid, but embodying into the living law of the College some formal acknowledgment of what has been growing up very slowly as custom—an attempt to place a very much greater responsibility on the Governors for the selection of Associates and for following the career of the Associates and drawing up recommendations concerning their elevation to Fellowship."

DR. A. B. BROWER: "From my own experience as a Governor some years ago, and I think it parallels the experience of most Governors, I knew relatively little about what goes on at the Governors' and Regents' meetings, and little of what the Credentials Committee was thinking about. Most new Governors have had little experience or knowledge of the inner workings of the organization. Setting up of plans should be left, I think, with the Board of Governors; I believe they should appoint an indoctrination committee. All new Governors would get together with this group; they would go over the experiences of this informed committee. I believe the final decision as to how a Governor is going to carry on in his state should be left largely to him, but we certainly could give him a number of wonderful suggestions that would be helpful. I suggest an indoctrination committee appointed by the Chairman of the Board of Governors."

SECRETARY E. R. LOVELAND: "On the Agenda of the next meeting of the Board of Governors is an excellent recommendation from Governor Elbert L. Persons for the publication of a booklet of detailed suggestions and instructions to all new Governors—in fact, to all Governors. Perhaps that Board will implement this practical suggestion."

PRESIDENT PINCOFFS: "I agree that the Governors should pursue a course of indoctrination, indoctrinating each other. To me the important principle that perhaps should be embodied in some motion by the Regents is that weight should be given to the Governors' recommendations. More weight and more responsibility should be given to the Governor in this matter of selection to Associateship and advancement to Fellowship. With that greater responsibility would come the need, perhaps, in some cases, of more ample facilities for determining in detail the candidate's qualifications."

DR. ASA L. LINCOLN: "Mr. President, the American College of Surgeons has gone through this problem, and it seems to me they have found a solution which is useful, certainly for larger metropolitan areas. They have local Credentials Committees, and, depending on the size of the community—in New York City, for example, they have one for the city environs and they have two preliminary committees —one a Committee on Applicants for Fellowship, consisting of ten members—all applications are considered by this Committee first. After that preliminary screening, before which each applicant appears in person, the Committee meets about once a month, those selected are recommended to a second Committee, which is called the New York City Credentials Committee, consisting of forty members. Certainly in their judgment they can get a much better line on candidates. It seems to me there should be some informal suggestion to Governors in large communities, where so many applicants are coming up, that more than just a few advisers are needed. When I was Governor, the large borough of Brooklyn furnished a large proportion of our applicants. I didn't know any of these men personally. A group of Internists, I

think they called themselves the Brooklyn Society of Internists, volunteered to take over the investigation of every candidate from Brooklyn. The proposer and seconder for each candidate appeared before this Committee, and the qualifications of their candidate were carefully analyzed and discussed. The plan worked very well. I think in metropolitan areas you need very much more than a half a dozen advisers."

Dr. Marion A. Blankenhorn: "Mr. President, the newly elected Governors may be in office quite some time before they can meet for indoctrination. Since indoctrination is what we want to implement, may I offer a resolution to the Regents that we suggest to the newly elected Governors that immediately on accepting their positions as Governors, that they write to the President and inform him of their program of seeking advice about the qualifications of candidates for Associateship and Fellowship, and that they inform the President of their methods of communication, communicating information to the Credentials Committee, over and above the ordinary printed form."

President Pincoffs: "The fact that the Governors are to consider this matter at their next meeting, what they decide on the booklet of instructions, is a decisive factor. I question, therefore, unless some one wishes to discuss it from another angle, since the resolution was not seconded, whether we Regents should devote more time to this this afternoon."

Dr. Burgess: "I suggest that the Regents go on record as encouraging the Board of Governors in this work of indoctrination. We all know the problem various states have, problems that differ from other states. All the Regents can do is to express their confidence and encouragement to the Board of Governors in doing this work."

President Pincoffs: "As an expression from the Regents to the Governors—and we will defer further consideration on this matter until another time.

"We shall proceed with the published Agenda. Next item for discussion is the James E. Paullin Scholarship Fund. The Regents previously adopted a resolution providing that the President and the Executive Committee determine upon the amount to be contributed by the College, and suggested that any individual, Regent, Officer, Governor or Member, who might be inclinded to send a personal contribution to this Fund be encouraged to do so through the College Office. In connection with that the President circulated a letter to the members of the Executive Committee; of the seven answers received, four were against in principle the College contributing to the Fund, although they all expressed the hope that individual donations might come in and go out from the College. They did not, however, think the principle was good to expend College funds for memorials to members—even for such a member as Dr. Paullin and such a worthy cause as the Scholarship Fund. The decision then of the Executive Committee was against College funds being supplied for that purpose. The hope was expressed that individual contributions might be raised above the total now contributed. $335.00 was contributed through the Executive Secretary's Office, and we would hope to bring it up to a larger total.

"May we now have the report of the Secretary-General, Dr. Richard A. Kern?"

Dr. Richard A. Kern: "Mr. President, Regents and Governors, since the last meeting of the Board of Regents, we have lost by death 34 Fellows and 4 Associates, to wit:" (read list of names and date of death).

President Pincoffs: "Will the members stand a moment in memory of those who have left us?"

. . . The Governors and Regents rose in memory of the deceased members. . . .

Dr. Kern (continuing): "Also, since the last meeting of the Board of Regents, 74 additional Fellows have become Life Members, making a grand total of 1,023, of whom 102 are deceased, leaving a balance of 921. The new Life Members, listed in the order of their subscription, are as follows:" (read list).

President Pincoffs: "May we now have the report of the Committee on Credentials, Dr. George Morris Piersol, Chairman?"

DR. GEORGE MORRIS PIERSOL: "Mr. President, members of the Board of Regents, since the last meeting of the Board of Regents the Committee on Credentials has held two meetings:

"(1) At the College Headquarters on March 15–16, 1952, with Doctors Lathrope, Yater, McGee, Wilson and Piersol in attendance, and with Dr. Richard A. Kern substituting for Dr. Kinsman, who was absent on account of illness;

"(2) At Cleveland, April 19, 1952, with Doctors Lathrope, Yater, Kinsman, McGee, Wilson, and Piersol of the Committee in attendance, and with the Secretary-General, Dr. Kern, the President-Elect, Dr. Miller, and four Governors, General Armstrong, Dr. Clark, Dr. Wright and Dr. Howard sitting in as guests.

"At the first meeting the Committee recommended the extension of the Associate term of Colonel Santino Joseph Lerro, (MC), USA, an Associate who is on military duty outside of the United States and thus is prevented from taking the examinations of the American Board of Internal Medicine and otherwise delayed, because of such service, in fulfilling the requirements for Fellowship within his normal term, the extension to be for as long a period as he is on military service outside of the United States.

"At the second meeting the Committee recommended the extension of the Associate term of Dr. Saul Rosenthal Kelson, New York, N. Y., until the spring of 1953, because of illness.

"Those two recommendations require the approval of the Board of Regents."

DR. SLOAN: "I move that the recommendations of the Committee on Credentials concerning Colonel Santino Joseph Lerro, (MC), USA, and Dr. Saul Rosenthal Kelson, New York, N. Y., be approved."

DR. HAROLD H. JONES: "I second the motion."

. . . The motion was put to vote and carried. . . .

DR. PIERSOL (continuing): "At the two meetings of the Committee the credentials of 231 candidates for Fellowship and 276 candidates for Associateship were reviewed. A summary of the recommended action of the Committee is as follows:

Candidates for FELLOWSHIP:		
Recommended for Advancement	159	
Recommended for Direct Election	8	167
Recommended for Election First to Associateship		6
Deferred		49
Rejected		9
		231
Candidates for ASSOCIATESHIP:		
Recommended for Election	212	
Recommended for Election as Associates, although proposed for Direct Fellowship	6	218
Deferred		52
Rejected		12
		282
Less: Direct Fellow candidates recommended for Associateship		6
		276

"The Committee has placed in your hands the list of 159 candidates for advancement to Fellowship, of 8 candidates for Direct Election to Fellowship (total, 167), and moves their election."

DR. BROWER: "I second the motion."

. . . The motion was put to vote and carried, electing the following group of candidates to Fellowship: (list previously published in the May, 1952, issue of this journal).

DR. PIERSOL (continuing): "The Committee has placed in your hands the list of those recommended to the Board of Regents for election to Associateship, a total of 218, and now moves their election."

DR. YATER: "I second the motion."

. . . The motion was put to vote and carried, electing the following group of candidates to Associateship: (list previously published in the May, 1952, issue of this journal).

DR. PIERSOL (continuing): "The following Associates elected April 27, 1947, ordinarily would now be automatically dropped, because they have presented inadequate or no credentials. In a technical sense they are dropped under the laws of the College, but if the amendment extending Associate terms to ten years is adopted, there may be some action taken on Friday to facilitate their being granted a reprieve: (read list of thirty names).

"In addition, there are certain miscellaneous Associates elected prior to April 27, 1947, whose terms were extended, due to military service or illness, until the spring of 1952, but in spite of that extension they have failed to qualify for advancement to Fellowship and must now be dropped, under regulations of the By-laws (date indicates when they became Associates): (read list of four names).

"All these men, their time had already run out before this meeting, had already been given special consideration because of extenuating circumstances, but in spite thereof, their time has run out."

PRESIDENT PINCOFFS: "Does your recommendation carry for the deferment of any decision on this latter group?"

DR. PIERSOL: "No, they couldn't help but be dropped. They have already been given special consideration and extensions, and those have expired."

DR. STURGIS: "Mr. President, I rise to a point of order. I think all of these ought to have a total of at least ten years."

DR. KERN: "I suggest everybody elected in the last five years should have an extension to ten years."

PRESIDENT PINCOFFS: "We earlier took action to defer action on the list of Associates who are automatically dropped at the end of five years until the Friday meeting of the Board. This is quite a small list—one was elected ten years ago, one seven and two six. I suggest we defer action until Friday. There has been no motion to drop them."

DR. PIERSOL: "It doesn't need a motion; it is automatic; it is required in the present By-Laws."

. . . On motion by Dr. C. C. Sturgis, seconded by Dr. Charles A. Doan, and passed, a resolution was adopted to defer action on them now until the Friday meeting, April 25, 1952. . . .

PRESIDENT PINCOFFS: "Next is a report on the Joint Commission on Accreditation of Hospitals by the Chairman of our representation, which includes Doctors Burgess and Middleton, all of whom have labored together in this difficult matter, Dr. LeRoy H. Sloan."

DR. SLOAN: "The Joint Commission on Accreditation of Hospitals is now officially organized, with headquarters in Chicago. It is made up of twenty members, six from the American Medical Association, six from the American Hospital Asso-

ciation, three from the American College of Physicians, three from the American College of Surgeons, two from the Canadian Medical Association. All expenses are divided according to that proportional setup. The Committee has labored very long; it has had many sessions, and the Advisory Committee also has had many meetings. It is now officially constituted and operating, as of September 1. Dr. Gundersen, of the American Medical Association, is the Chairman, Dr. Sloan is the Vice Chairman, and Mr. Hummel is the Secretary-Treasurer. After much labor, Dr. Edwin L. Crosby, Director of Johns Hopkins Hospital, has been elected the Director of the Commission and has accepted, the appointment to take effect officially September 1."

DR. STURGIS: "I am aware of the great deal of work that this Committee has done, and I think it is one of the most important things the American College of Physicians ever accomplished. I move a vote of thanks on behalf of this Board to Dr. Sloan, Dr. Burgess and Dr. Middleton for this very fine contribution."

DR. MCCARTHY: "I second the motion."

. . . The motion was put and carried. . . .

President Pincoffs called upon the Secretary to read a series of important announcements, and there being no further business, the meeting adjourned at 4:30 p.m.

Adjournment.

Attest: E. R. LOVELAND,
Secretary

MINUTES ANNUAL BUSINESS MEETING

CLEVELAND, OHIO

APRIL 24, 1952

The 1952 Annual Business Meeting of the American College of Physicians, during the 33rd Annual Session, was held on April 24, 1952, convening at 2:00 p.m., at the Cleveland Public Auditorium, Cleveland, Ohio, with President Maurice C. Pincoffs presiding.

The President declared a quorum of Masters and Fellows; Mr. E. R. Loveland, Executive Secretary, read the Minutes of the last Annual Business Meeting, which, by resolution, were approved as read.

Dr. Richard A. Kern, Secretary-General, presented the following amendment to the By-Laws, which had been previously approved by the Board of Regents in accordance with regulations governing amendments to the By-Laws:

"AMENDMENT TO THE BY-LAWS

"Term of Associateship and Eligibility for Fellowship

"ARTICLE VII, Section 4. Candidates so elected shall be continued as Associates for a term not to exceed *ten* years.

"An Associate will be eligible for election to Fellowship at the end of three years. Upon expiration of this three-year period, he shall be notified in writing by the Committee on Credentials of his eligibility for election to Fellowship during the next *seven* years, provided he has met the requirements necessary for Fellowship within that time. If he is not elected to Fellowship within *ten* years of election to Associateship, his Associateship is automatically terminated. The Committee on Credentials, with the approval of the Board of Regents, shall be given discretionary power to modify this ruling under exceptional conditions."

Dr. Kern moved the adoption of the amendment, and Dr. Cyrus C. Sturgis seconded the motion.

President Maurice C. Pincoffs then presented an interpretation of the Amendment as applied to present and future Associates of the College, as follows:

"INTERPRETATION

"(1) All future Associate candidates when elected will serve a minimal term of three years or a maximal one of *ten* years.

"(2) The term of present Associates shall be extended to a maximum of *ten* years.

"(3) Associates whose terms expired April 20, 1952, and who have been dropped at that meeting by action of the Board of Regents, or whose resignations have been accepted within the past year, shall have the privilege of applying in writing to the Committee on Credentials for reinstatement as Associates for such period as is required to make their total term of Associateship ten years. Each such request must be considered by the Committee on Credentials after approval has been obtained preferably from the original proposer and seconder of the candidate and by endorsement of the appropriate Governor. If

favorably acted upon by the Committee on Credentials, such Associates may be officially reinstated by the Board of Regents.

"(4) Associates whose terms expired prior to and including November, 1951, and who were dropped or whose resignations were accepted by the Board of Regents must, if they desire to re-enter the College, be re-proposed in the regular manner and, if re-elected, will serve a minimum three-year term or a maximum ten-year term."

The motion was then put to vote and carried.

Dr. William D. Stroud presented the annual Treasurer's Report, as follows:

"Mr. President, Masters and Fellows of the College: The detailed Statements of Operation of the College for 1951, along with the Certified Public Accountant's report, will be published in an early issue of the ANNALS OF INTERNAL MEDICINE.

"During the year 1951 the College added to its General Fund, $95,845.75; Endowment Fund, $13,246.18; A. Blaine Brower Fund, $10,000.00, and Restricted Funds $725.49; total, $119,817.42.

"The Gross Assets of the College, as of December 31, 1951, amounted to $886,719.92, divided as follows:

General Fund	$508,144.00
Endowment Fund	347,079.60
James D. Bruce Fund	10,000.00
A. Blaine Brower Fund	20,000.00
Restricted Funds	1,496.32
	$886,719.92

"The assets of the College have increased one hundred times over what they were at the reorganization of the College in 1925–26, yet the membership dues are the same today as they were at that time—perhaps, the only medical society on record that can make that statement.

"The College operated wholly within its Budget during the past year. In fact, the income exceeded budgetary expectations, whereas expenditures were less than the appropriations. The investments of the College are supervised by a competent Investment Counselor and by the Committee on Finance, and are carefully reviewed periodically. As of December 31, 1951, the College held Investments at Book Value totalling $720,610.96, and, as of March 28, 1952, showed an appreciation of $116,050.04. The average yield for 1951, based on current market value, was 4.35%, but considerably greater when based on cost.

"The Board of Regents has approved a Budget for 1952 calling for an estimated Income of $335,090.00 and an estimated Expenditure of $285,261.00, leaving an estimated balance of approximately $50,000.00.

"The financial policies of the College continue to be conservative at all times.

Respectfully submitted,

WILLIAM D. STROUD, *Treasurer.*"

On motion by Dr. Charles A. Doan, seconded by Dr. Edward L. Bortz and put to vote, the Treasurer's Report was accepted.

Mr. E. R. Loveland, Executive Secretary, presented the annual Executive Secretary's report, as follows:

"Mr. President, Fellows and Masters of the College: the report of the Executive Secretary is supplementary to those of the President, the Treasurer and the Secretary-General.

"The ever increasing volume of College activities is carried on with meticulous care in a sense of deep responsibility, but we have reached the point where it is utterly impossible for one individual to answer personally all of the letters of our members and to attend personally to all the problems that are presented. Consequently your Executive Secretary finds it necessary to delegate to his assistants a proportion of the work for which they are being trained. The handling of proposals for membership, and matters relating thereto, are handled by Mr. H. Kurtz Canby; matters concerning advertising in the ANNALS are handled by Mr. Frank M. Shanbacker, a new addition to our staff; and a great many general responsibilities are assigned to Miss Ott. Of course, our work requires a considerable number of additional assistants—addressograph operators, stenographers, typists and clerks.

"We have a large number of very active Committees, to the members of which we should all be very grateful for their contributions of time and thoughtful work. Many of these Committees, especially the Committee on Credentials, the Committee on Postgraduate Courses and the Committee on Fellowships and Awards, perform an enormous amount of work throughout the year for the College. Their programs could not be so outstandingly successful otherwise.

"I am gratified to report to our members that the past year has been one of continuing success in every department. Even a larger number of physicians have registered for our Postgraduate Courses; this Annual Session is larger than that of last year; the circulation of the ANNALS has increased by more than fifteen per cent; membership continues to expand; an increasing number have become Life Members; the Endowment Fund and the General Fund have grown; the Regional Meetings have been highly successful; our fellowship programs, including the Research Fellows and the Latin-American Fellows, have been thoroughly successful; we have increased our Brower Traveling Scholarships to two, and wish there might be more available; the Directory of the College, containing more than eight hundred pages, has been revised and republished, and a Supplement thereto will be published during the coming summer; and those who have been in charge of the Program of this Annual Session have instituted some changes and presented a program of real excellence.

"At this point, I should like to bespeak your support of our fine Technical Exhibit by urging you to take the time to stop by and inspect the exhibits. Ours is no ordinary Technical Exhibit; it is conducted on a different plane. It is required that both the firm and their exhibits shall be accepted by our Committee on Exhibits. It is also required that we exclude all products which have no relevancy to the field of Internal Medicine and its allied specialties. There are no exhibits that are taken just for financial income. You will find no cigarettes, ginger ale, and such other irrelevant products here. We want to conduct an Exhibit that will command your respect and will be valuable in keeping you informed of both old and new products, and to provide a contact for service on products or equipment that you may be using. The exhibitors contribute some $38,000.00 toward the cost of our Meeting, and it is but a small favor to extend them courteous and interested attention.

"It has been a great privilege to work this past year with our President, Dr. Pincoffs. He is conservative, always holding the highest ideals for the College and for its services to its members and to medicine. He has contributed a great deal of his time, in addition to his heavy burdens as Editor of our journal and his regular responsibilities in Baltimore, to the College; has gone far and near to its Regional Meetings, and has been a source of inspiration to us all.

"We are deeply appreciative of the help and counsel of all our Officers, our Regents and our Governors who have so unselfishly given of their time, service and thought to the College.

"We have just received from the Registration Desk a report that the total registration to this time at this meeting is 4,436 of which 684 are ladies.

Respectfully submitted,

EDWARD R. LOVELAND, *Executive Secretary.*"

On motion duly seconded and carried, the report of the Executive Secretary was accepted.

Dr. Richard A. Kern then presented the annual report of the Secretary-General, as follows:

"Mr. President, Regents and Governors, Masters and Fellows of the College: This report will be limited to certain important matters of especial interest to you

"Membership: Since the last Annual Session of this College, there have been elected 1 Master; 297 Fellows; 443 Associates, which brings the total membership to the following:

Masters	13
Fellows	5,439
Associates	1,898
Total	7,350

"Life Members: During the past year 96 Fellows have become Life Members of the College, bringing the total to 1,023, of whom 102 are deceased, leaving a balance of 921.

"Deaths: Since the last Annual Session we have lost by death 2 Masters, 65 Fellows and 12 Associates. Their names and records appear in the Archives of the College, and their obituaries have been published or will be published in the ANNALS OF INTERNAL MEDICINE.

"Postgraduate Courses: The Advisory Committee on Postgraduate Courses of the Governors and the Committee on Educational Policy of the Board of Regents organized and conducted during 1951 a total of 17 courses, with a registration of 1,113 physicians, a small increase over that for the preceding year. The Committee is attempting to expand the field of study and to increase and diversify the institutions and geographical locations where courses are given. This program is one of our most popular activities. The Board of Regents has approved the schedule of courses, as recommended by the Committee, for the autumn of 1952 and the spring of 1953, and will announce these schedules in an early issue of the 'ANNALS OF INTERNAL MEDICINE' and in the next issue of the Postgraduate Bulletin.

"Fellowships: The College awarded six Research Fellowships for the period July, 1951, through June, 1952, but the programs of three have been delayed because of military service, their awards are being held for them pending their release from active duty. Four new Research Fellowships have been awarded for the period July 1, 1952, through June 30, 1953. The work of these fellows is carefully observed with a view to evaluating the program and to act as a guide in the future.

"The College also has sixteen Latin-American Fellows presently working in this country, this program being carried on in co-operation with the W. K. Kellogg Foundation who provide the funds. The program affords an unique opportunity for the training of Latin-American young men for careers of teaching and research in their homelands. Our Committee on Fellowships has been particularly successful and effective in eliciting the co-operation of important and competent men to act as Preceptors, and to these Preceptors and their institutions the College expresses a debt of gratitude.

"In 1950, through an Endowment Trust in the amount of $10,000.00, contributed by Dr. A. Blaine Brower, a Regent of the College, the Brower Traveling Scholar-

ships were established for the purpose of providing an opportunity for a worthy young physician, preferably an Associate of the College, to spend a month or more as a visiting fellow at some institution, or institutions, for observation and postgraduate study. The first award was made during 1951. The results were so gratifying that the College appropriated an additional $10,000.00 and established a second Brower Traveling Scholarship. Therefore, during 1952 two Traveling Scholarships have been awarded to Associates of the College, one of which has been concluded and the other is in course of arrangement through the Committee on Fellowships and Awards.

"Regional Meetings: During the calendar year 1951 twenty-three Regional Meetings, either State or multi-State, were held, with a total attendance of 2,668. Since the last Annual Session of the College, that is, during Dr. Pincoffs' presidency, there have been twenty-three Regional Meetings, with an attendance of somewhat over 2,600, the exact figure not being available because the attendance report for the last such meeting, held at Salt Lake City only on April 12, was not available when this report was prepared. The Regional Meeting programs are carried on by the Governors of the College, many of whom have already scheduled meetings for the current year and even into 1953.

"Perhaps of greatest significance to the members at large is the Annual Session of the College. This Session in Cleveland is a further outstanding example of the accomplishments of a year's co-ordinated effort. We are mindful and appreciative of the great efforts of those who have made this, the Thirty-third Annual Session of the College, possible.

Respectfully submitted,
RICHARD A. KERN, *Secretary-General.*"

On motion duly seconded and carried, the report of the Secretary-General was accepted.

DR. RICHARD A. KERN: "President Pincoffs, you have served this College long, faithfully and well in posts of increasing trust and responsibility, culminating in its highest office, the Presidency. You have given us able and constructive leadership, noteworthy for its steadfastness of high purpose, and administered with courtesy, understanding and infinite patience.

"A year ago the gavel became the symbol of your Presidential authority; today it becomes not only the token of our grateful appreciation of your outstanding service, but more especially the memento of the honor, esteem and affection in which you are held by the Fellows, Masters, Governors, Regents and Officers of the American College of Physicians. On their behalf, I am happy to present this gavel to you."

. . . Standing vote of applause. . . .

PRESIDENT MAURICE C. PINCOFFS: "Officers, Fellows and Masters of the College: I need hardly to tell you that I deeply appreciate the statements of our Secretary-General and this remembrance, which I shall always cherish, of my term as President. It has been for me a busy year and a year very rich in rewards. I have been enabled to see the College operating in many parts of the country and to make closer acquaintance with many of you whom I now look upon as friends as well as fellow members.

"I would not leave this office without expressing my deep appreciation of the advice, help and steadfast support I have received in so many parts of the country and, in particular, from our Governors, Regents and Officers, and from the magnificently managed office of our Executive Secretary, and from him himself.

"At this point I turn to call on Dr. T. Grier Miller. It is my privilege, Dr. Miller, to induct you into the Presidency of this College, to which you have been elected, and to turn over its responsibilities to you with this symbol of your authority" (presented Dr. Miller with the College gavel).

. . . Applause. . . .

PRESIDENT T. GRIER MILLER: "Dr. Pincoffs, Officers, Regents, Governors, Masters and Fellows of the College: In accepting the high office to which you have elected me, I wish, firstly, to thank you for the honor; secondly, to admit a certain feeling of inadequacy to meet the responsibilities, and, thirdly, to seek your coöperation and support in the challenges that face us during the coming year.

"Our College, in my opinion, is the most important organization of Internists in America. This is because of its educational objectives, its democratic principles and the inclusion in its membership of outstanding medical clinicians in each section of the United States, Canada and Central America. In spite, however, of the eminence of many of our Fellows as practitioners, teachers, investigators and lecturers, we must admit that we are not securing the admission to membership of some basically trained young men who are productive workers in the field of medicine and who are fast becoming its leaders. This is evident when one reviews the programs of our Annual Meetings and notes how many of the speakers, obviously outstanding Internists of the country, are not Fellows of this College. On the other hand, we are admitting to Associateship some young Internists, including many already certified, whom with deep regret and some embarrassment, we are having to drop from time to time because of failure to meet our requirements for Fellowship. This situation suggests the desirability of further study of the status of Associateship and of a reëvaluation of our criteria for Fellowship.

"Other special problems that face us at this time include an intensification of our educational efforts for the benefit of all aspiring Internists, irrespective of Associates, and continued activity in the fields of residency training and hospital accreditation.

"In accepting the chief responsibility for an effort to solve these and other College problems, I feel very humble. My years of service to the Board of Regents has acquainted me with the signal contributions that have been made by the past Presidents under whom I have served, Doctors Barr, Morgan, Palmer, Fitz, Middleton and, especially, Pincoffs. We all know of the even more significant contributions made by Doctors Stengel, Martin, Piersol and other earlier Presidents. I fully appreciate the increasing difficulty of adding to their accomplishments, yet steady progress must be made if we are to advance our enviable position in American Medicine.

"Consequently, I earnestly seek the forbearance and the coöperation of other Officers, the Regents, the Governors and in view of the heavy responsibility that also rests on them I seek for them as well as for myself the united support of all the Fellows and Masters and of our able Executive Staff. In anticipation of such help and I know that I can count on it, I pledge my best efforts to the task of maintaining and advancing the dignity, the prestige and the service of the American College of Physicians."

. . . Applause. . . .

President T. Grier Miller then called for the report of the Committee on Nominations by its Chairman, Dr. A. B. Brower.

(Dr. A. B. Brower presented individually the nominations for the Elective Officers, members of the Board of Regents and members of the Board of Governors, each group being acted upon separately and in accordance with the provisions of the Constitution and By-Laws. The detailed list is not herein published, because of previous publication in the May, 1952, issue of this Journal.)

President T. Grier Miller requested Dr. Harold H. Jones and Dr. Asa L. Lincoln to escort the new President-Elect, Dr. LeRoy H. Sloan, to the platform.

PRESIDENT-ELECT LEROY H. SLOAN: "Mr. President, Dr. Pincoffs, Masters and Fellows: I am deeply grateful of the honor which has been paid me today. I am mindful not alone of the honor, but also of the responsibility which the duty of President entails. I accept the responsibility as a recognition of the part which the bedside practitioner in home and hospital and part-time teacher must occasionally play in the conduct of the affairs of this College at top level.

"I am cognizant of the pattern of progress and the clear-cut path of advance which my distinguished predecessors have cut out for me to walk in. I shall neither step out of character nor attempt to impress you with hitherto unrecognized arrogation.

"The function of the College is the prosecution of continuing graduate medical education. Fortunate we are in the heritage left by our loyal and far-seeing forbears; fortunate we are in a central headquarters staff, and when the reins are turned over to me next year by our able new President, Dr. Miller, I shall devote whatever ability the good Lord has conferred upon me to protect this heritage, so that at the end of a short year you may all feel that the job has been well done and that knowledge has grown from more to more and the life of the College made richer. Thank you!"

. . . Applause. . . .

PRESIDENT MILLER: "Newly elected Governors who have not served previously, or other Governors who may be interested, are invited to meet immediately at the end of this afternoon's General Session in the Regents-Governors Room with the Chairman of the Committee on Credentials, the Chairman of the Board of Governors, the President of the College and the Executive Secretary.

"Secondly, I wish to announce that the 1953 Annual Session of the College will take place in Atlantic City, N. J., April 13–17.

"There is a resolution, I believe, to be presented by Dr. J. Owsley Manier."

DR. J. OWSLEY MANIER: "Mr. President, Masters and Fellows of the College: I wish to present to you the following resolution of thanks to those to whom we are so deeply indebted for the excellent program and pleasure we have had at this meeting:

"To our distinguished leader and President, Dr. Maurice C. Pincoffs, for the inspiration of his guidance during the past year and for the superior program of Morning Symposia and General Sessions at this meeting;

"To his Chief of Staff, General Chairman Roy W. Scott, for the organization of this meeting and for his part of the magnificent program;

"To the Assistant General Chairman, Dr. Fay A. LeFevre, and to the Chairmen of the local Cleveland Committees:

Dr. Walter M. Solomon, Chairman of the Committee on Auditorium
Dr. Joseph M. Hayman, Jr., Chairman of the Committee on Hospital Clinics
Dr. John E. Rauschkolb, Chairman of the Committee on Hotels and Transportation
Dr. Harry D. Piercy, Chairman of the Committee on Entertainment
Dr. A. Carlton Ernstene, Chairman of the Committee on Panel Discussions
Dr. Charles S. Higley, Chairman of the Committee on Publicity
Dr. John D. Battle, Jr., Committee on Televised Clinics,

and to the individual members of each of those Committees;

"To Mrs. A. Carlton Ernstene, Chairman of the Committee on Ladies' Entertainment, and all of her worthy and capable colleagues;

"To Dr. Charles D. Dawe, Director of the Orpheus Male Chorus, and to Dr. Jerome Gross, Violinist, for a most unusual entertainment which they afforded at our Monday Concert;

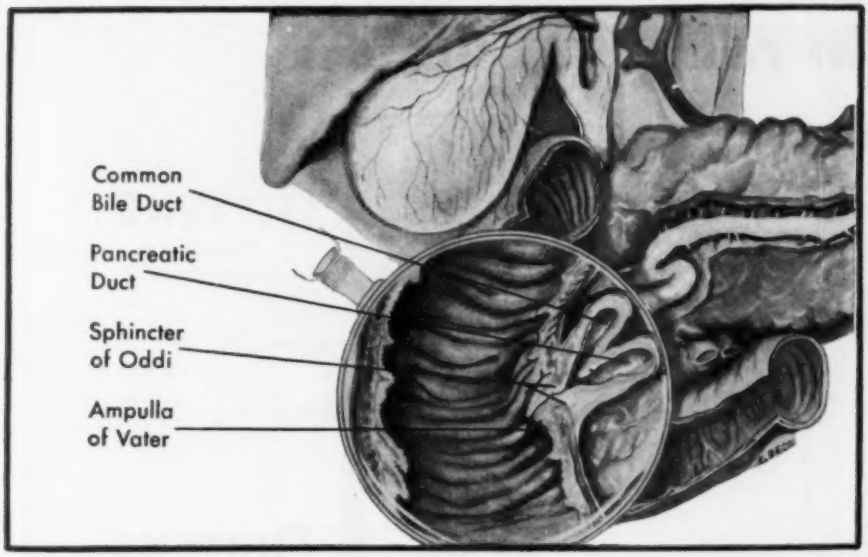
"To Mr. Edward C. Brennan, Executive Vice President of the Cleveland Convention and Visitors' Bureau, and to his assistants;

"To all of these and many others, individually and collectively, our heartfelt thanks again for their manifold contributions to the success of this memorable meeting and for their most generous hospitality."

On motion by Dr. J. Owsley Manier, seconded by Dr. Cyrus C. Sturgis, and carried, the resolution was enthusiastically adopted.

Adjournment.

Attest: E. R. LOVELAND,
Secretary



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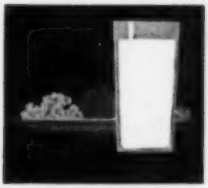

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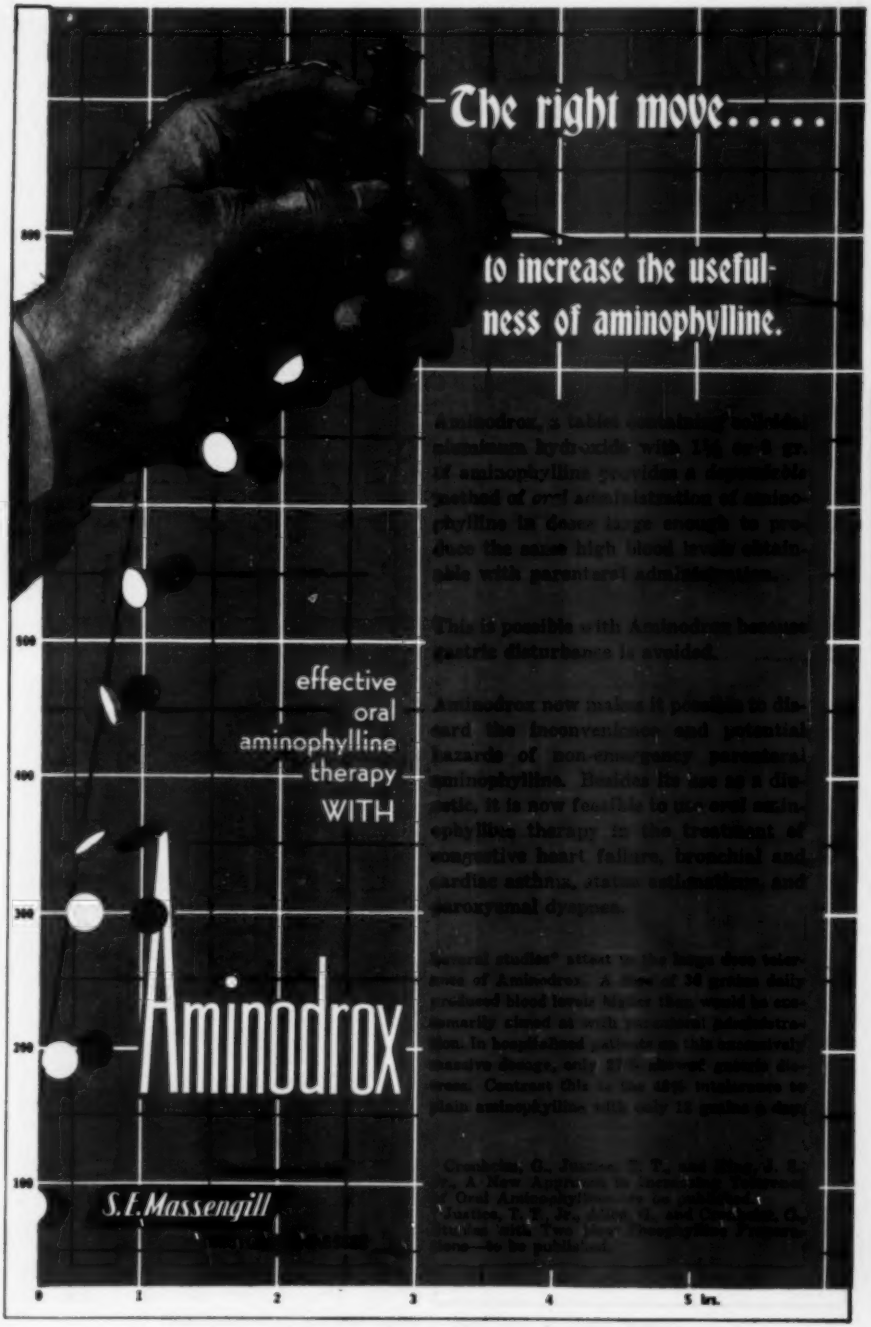
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1. Angiology 3:1 (Feb.) 1952.
2. Angiology 3:16 (Feb.) 1952.

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1. Meyer, K. et al. Am. J. Med. 5:482,1948. 2. Wang, K. J. and Grossman, M. I. Am. J. Phys. 155:476,1948. 3. Grace, W. J. Am. J. Med. Sc. 217:241,1949; 4. Hufford, A. R. Rev. of Gastroenterology, 18:508, 1951.

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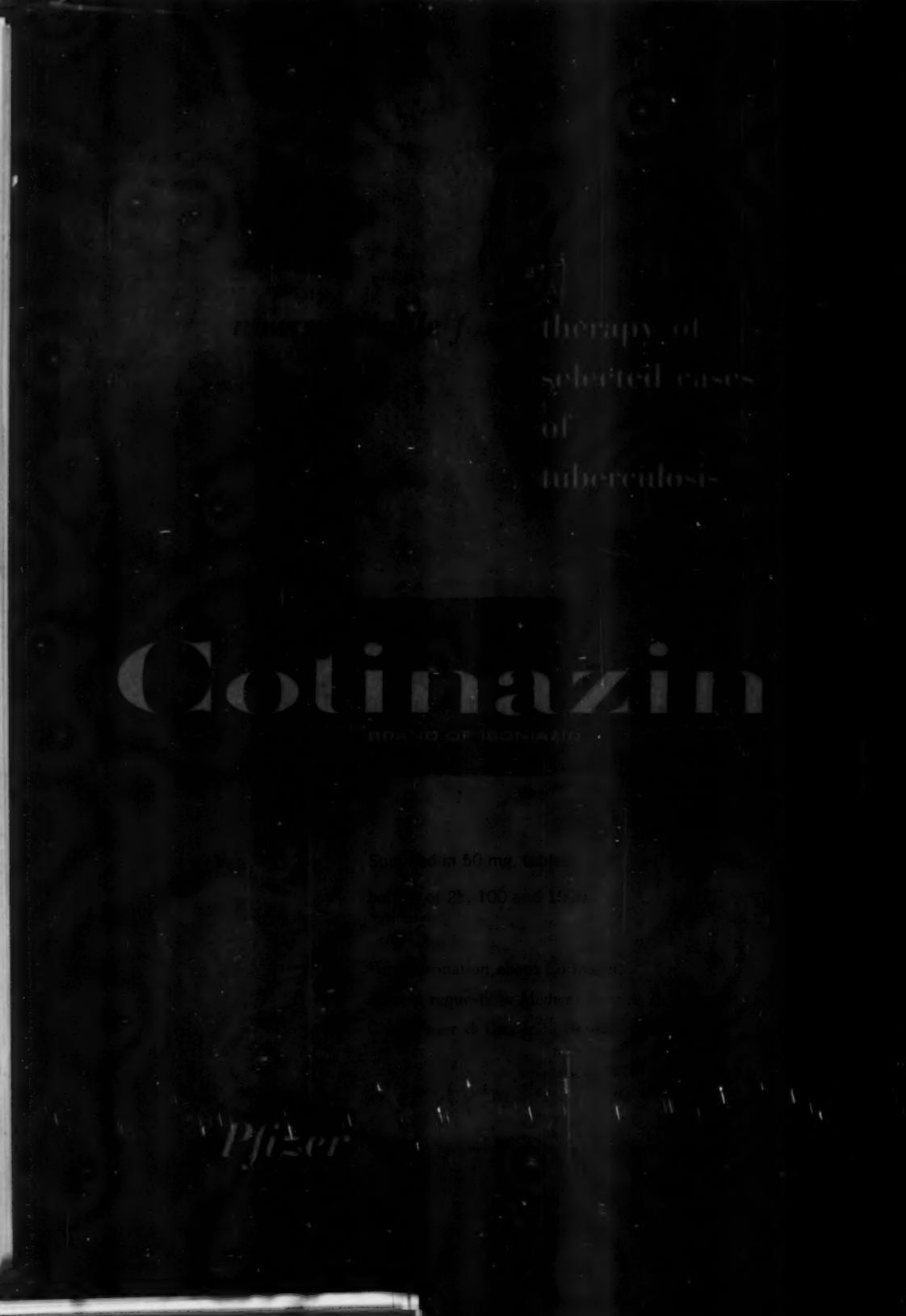
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